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The Journal of
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Further Observations on the Value of the Pregnandiol Test for Pregnancy[1]

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OBSERVATIONS on the excretion of pregnandiol in the urine of women, relative to corpus luteum activity and progesterone secretion, have led to the conclusion that *the presence of pregnandiol in the urine during amenorrhea signifies a normal pregnancy* (3, 10, 17). On this basis we presented in 1944 a simple, rapid method for the determination of pregnandiol in urine (color reaction) as a diagnostic test for pregnancy (9).

The present report summarizes data on 248 patients, of which 155 were tested since the previous report. The results indicate that the pregnandiol color reaction is at least as accurate a diagnostic test for pregnancy as is the Friedman test. Added experience has led to technical refinements which improve the reliability of the procedure.

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[1] Aided by funds from the Committee on Scientific Research of the American Medical Association granted to Dr. Rachmiel Levine.
[2] The department is in part supported by the Michael Reese Research Foundation.

FURTHER OBSERVATIONS ON THE TECHNIQUE OF THE TEST

The technique for the pregnandiol determination has been detailed elsewhere (9). The entire procedure requires two and one half to three hours to complete. From four to six specimens can be conveniently tested simultaneously. The chemicals are inexpensive, and the equipment employed is standard in clinical laboratories. No animals are needed. The rapidity and economy of the determination are self-evident.

From further accumulated experience, it has been found practical to take several precautionary measures to insure against interference with the final color reaction, viz.:

1. New reagent solutions should be tested for their production of spurious colors. Each solution, in the volumes employed in the test, is evaporated to dryness in the hood. Ten cc. of conc. H_2SO_4 is added to the cooled residue of each solution. Any solution giving a visible color reaction with the conc.

H_2SO_4 must be discarded and be prepared anew or redistilled.

Commercial absolute alcohol has contributed to false color reactions. Preparation of absolute alcohol from commercial absolute alcohol by the method of Lund and Bjerrum (12) has eliminated the misleading color factor.

2. Preparation of 2 per cent NaOH in absolute methanol solution for use over a long period of time has led to "false negative" reactions. This solution is now prepared in the laboratory as follows:

a) A solution of from four to eight per cent NaOH in methanol is prepared in a *dry* Erlenmeyer flask.

TABLE 1. SUMMARY OF RESULTS[3]

Clinical state	Pregnandiol test		Friedman test	
	Correct	Incorrect	Correct	Incorrect
Normal pregnancy	116	8	96	12
Amenorrhea (not pregnancy)	106	9	75	9
Corpus luteum cyst	0	1	1	0
Hydatid mole	3	0	0	3
Syncytioma	1	0	0	1
Testicular tumor	4	0	3	1
Total	230	18	175	26
Accuracy	92.7%		87.1%	

[3] All patients checked by clinical follow-up.

b) The mixture is filtered through a *dry* sintered glass filter to remove the precipitated carbonate.

c) The NaOH concentration of the filtrate is determined by titration with N/10 H_2SO_4.

d) The filtrate is then adjusted to a concentration of two per cent with absolute methanol.

e) The solution is *freshly* prepared every two to three days.

3. Neglect in observing the final stages of the toluene or ethanol evaporation [steps B-7 and D-4 of the "Technique" (9)] may result in puzzling color reactions. Charring of the residues has led to dull, dirty, and light brown colors. These are easily distinguished from the true color reaction. The use of a fine stream of air to eliminate the last traces of liquid from the vessel, which has been removed from the hot-plate, hastens evaporation and prevents charring.

Experience has led us to change the standard for a "positive" color reaction. Previously only an orange color was considered "positive." Quantitative studies using a spectrophotelometer indicate that an orange color is equivalent to 1 mg. of pregnandiol per 100 cc. of urine,[4] or an excretion of approximately 15 to 20 mg. of pregnandiol per 24 hours. This range is higher than that reported in very early pregnancy (1) (2), and a standard based upon such an excretion would and did lead to false "negative" results. Therefore, the standard has been fixed at a color equivalent to a 24-hour pregnandiol excretion from 6 to 8 mg. The new minimum "positive" color is deep yellow.

RESULTS

The first morning urine specimens of women with amenorrhea, who presented obstetrical diagnostic problems, were examined by the pregnandiol color reaction and by the Friedman test. The urine of males who had testicular tumors was also similarly tested.

Table 1. summarizes the results obtained in 248 patients. Of these, 124 had normal pregnancies. Results were recorded as correct in 116 cases and incorrect in eight cases. "Positive" color reactions were obtained as early as five days after the first missed period, and more than 60 per cent of the patients were tested in the first four weeks after the missed period (see Table 2). Some of the patients in this group, prior to the pregnancy, exhibited abnormalities such as irregular menses, functional sterility, fibromyomata, and pulmonary tuberculosis.

The Friedman test was "positive" in 96 cases. Twelve errors were recorded, two occurring as late as the third month of pregnancy.

[4] In the procedure employed, Na pregnandiol glycuronidate is hydrolyzed. The color reaction is a measure of the total pregnandiol excretion (free plus combined). Data pertaining to pregnandiol excretion (1, 2) represent gravimetric determinations of Na pregnandiol glycuronidate which are expressed in terms of pregnandiol.

In the 115 patients with amenorrhea in whom suspected pregnancy was later ruled out, the pregnandiol color reaction was found correct in 106, and incorrect in 9. Table 3. lists the results obtained in this group according to clinical diagnosis.

Eight "false positive" results were recorded in four groups of patients (two in each group). Among these groups were those with (1) delayed menses, (2) irregular menstrual cycles, (3) fibromyomata, and (4) early menopause. Four of these eight also showed "false positive" Friedman tests. A correct evaluation of the cause of these errors is not possible at present.

The occurrence of corpus luteum cysts has been suggested as a source of incorrect "positive" reactions. The presence of one such case in this series emphasizes its infrequent occurrence. The color reaction became negative two days after the surgical removal of the corpus luteum cyst.

The diagnosis of "ovarian cyst" was made in five additional patients, but pregnandiol was not present in the urine.

It has been demonstrated that the urines of patients with hydatid mole give strong positive Friedman reactions due to the excretion of large amounts of luteinizing hormone and contain small amounts of pregnandiol. The three patients tested in this series (Table 1.) did not excrete sufficient pregnandiol to give a "positive" reaction. Histological examination of the uterus, removed from a woman in whom a hydatid mole was suspected, revealed the presence of a syncytioma—a tumor of the chorion. The color reaction prior to hysterectomy was "negative," the Friedman test "positive." It is believed that the syncytioma should be grouped with other chorionic neoplasms, such as the hydatid mole and chorionepithelioma.

Four patients with testicular tumor were encountered among the males, and these gave uniformly "negative" pregnandiol reactions. A patient with a dysgerminoma in this group gave a "positive" Friedman test.

The use of the pregnandiol color reaction in the prognosis of threatening abortion [noted in our previous publication (9)] has been extended and will be reported at a later date.

TABLE 2. PATIENTS WITH NORMAL PREGNANCY GROUPED ACCORDING TO DURATION OF AMENORRHEA

Menses overdue	Pregnandiol test		Friedman test	
	Correct positive	Incorrect false negative	Correct positive	Incorrect false negative
1 week	15	0	13	3
2 weeks	28	2	24	4
3 weeks	12	1	12	0
4 weeks	14	4	14	3
More than 4 weeks	26	0	11	2
Not known	21	1	21	0
Total	116	8	95	12

TABLE 3. CLASSIFICATION OF THE NON-PREGNANT AMENORRHEA GROUP

Clinical diagnosis	Pregnandiol test		Friedman test	
	Correct negative	Incorrect false positive	Correct negative	Incorrect false positive
Delayed menses	38	2	25	4
Menopause	11	2	8	0
Irregular menses	6	2	3	0
Fibromyomata	2	2	2	2
Ovarian cysts				
(a) Corpus luteum	0	1	1	0
(b) Paraovarian	1	0	1	0
(c) Chocolate cysts	1	0	1	0
(d) Polycystic ovaries	1	0	1	0
(e) Unclassified	2	0	0	1
Hypothyroidism	4	0	3	1
Lactation	2	0	1	0
Tuberculosis	1	0	—	—
Pelvic inflammatory disease	2	0	1	0
No diagnosis	35	0	28	1
Total	106	9	75	9

DISCUSSION

The present report summarizes the experience to date in this laboratory with the pregnandiol color reaction as a diagnostic test for pregnancy. The results indicate that the color reaction is at least as accurate as the Friedman test.

The accuracy obtained in this laboratory with the Friedman test (87 per cent) is not as high as most investigators report. Davis and Walker (5), Friedman and Lapham (7), Magath and Randall (13), Reinhart and

Scott (14), Sondern and Silverman (16), Ziserman (18), to list a few, recorded accuracies of 92 to 99 per cent. In a review of the literature, King (11) found variations in accuracy from 84 to 100 per cent. Davy and Sevringhaus (6) emphasize that early pregnancy and diagnostic problems relating to pregnancy should form the basis of analysis. With this in mind, they reported an error of 10 per cent in 425 patients tested by an immature rat method, the immature female rabbit and/or the Friedman technique.

The majority of the patients in the present series presented problems in diagnosis, and more than 60 per cent were tested in the four weeks after the onset of amenorrhea. It therefore becomes more understandable why the accuracy in this series with the Friedman test is lower than that usually reported.

The Smiths state (15), "... it is not sufficiently recognized by most practitioners that the pregnancy test—whatever method is used—is not infallible." This important practical dictum serves to emphasize the fact that a pregnancy test should be considered as an adjunct to clinical judgment in problems concerning the diagnosis of pregnancy. Physicians are inclined to be impressed by the stated accuracy of pregnancy tests and seem to forget that errors do occur (4).

In a thoughtful editorial review of pregnancy tests, Smith and Smith (15) state that "false negative" results would be expected with the pregnandiol color reaction, since "pregnandiol excretion in early pregnancy is frequently no higher than in the nonpregnant woman." It should be repeated and stressed that the pregnandiol color reaction as a diagnostic test for pregnancy is based on *the presence of pregnandiol in the urine of women who have missed at least one menstrual period.* The relative pregnandiol excretion, which the Smiths emphasize, is not the significant feature. From their objection one would expect "false positive" rather than "false negative" results to interfere with the accuracy of the color test.

By changing the minimum "positive" color to deep yellow as indicated above, the sensitivity of the test was increased and it became possible to evaluate this divergence of thought. The number of "false positive" reactions was not increased by this change in standard. Several results which would have been interpreted as "negative" by the older criteria were thus correctly judged to be "positive."

It has been asked whether patients with irregular menses might not give "false positive" results due to delayed ovulation or prolonged corpus luteum activity. In this series, the urine of twelve women who had irregular cycles was tested. Four patients had become pregnant and gave correct "positive" color reactions. Six who were not pregnant showed no pregnandiol in the urine. Two patients gave "positive" reactions which were recorded as incorrect. From this small series and these incomplete data it is not possible to state whether delayed ovulation had occurred, whether corpus luteum activity was prolonged, or whether an early pregnancy with subsequent abortion had not been detected clinically.

Failure to observe the precautions in performing the test indicated above may lead to incorrect results. Technique is important in such a chemical procedure. Therefore, the directions outlined, including the precautionary measures, should be followed closely.

Technically the procedure is simple and does not involve laborious, constant effort (8). There are steps where the test may be interrupted (B-7, C-3, D-4). Since six tests can be performed simultaneoulsy in three hours, the actual time devoted to each test is half an hour. In our hands this is less time than has been found necessary to devote to an individual Friedman test.

SUMMARY

Results of the pregnandiol color reaction test for pregnancy employed in 248 patients involving obstetrical diagnostic problems indicate an accuracy of 92 per cent. The accepted Friedman test was recorded as 87 per cent correct in this same series.

The advantages of the pregnandiol test are reemphasized in this report. Technical

refinements and precautionary measures are outlined.

The standard for a "positive" reaction has been altered to a deep yellow color which avoids "false negative" results and does not increase the incidence of "false positives."

The infrequency of the occurrence of proven corpus luteum cysts is indicated. It does not therefore affect the accuracy of this pregnancy test. Patients with hydatid moles and chorionic neoplasms do not excrete sufficient pregnandiol to give a "positive" reaction.

It is stressed again that the basis of the test is the presence of pregnandiol in the urine of women who have missed at least one menstrual period.

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Testosterone Propionate in Treatment of Senile Pruritus[1]

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IN RECENT years geriatrics has become an important part of medicine. Geriatrics may be defined as the study of the diseases of old age. Stieglitz (17) states that it is useful to consider that most of the clinical problems related to geriatrics start at about 40 years of age. The so-called degenerative disorders become more frequent at this period, and their menace is greatest in the years from 40 to 60. If health can be maintained during this critical time, the probability of long disability and uselessness because of chronic illness after the age of 60 will be greatly reduced. Bancroft (1) considers the age of 65 years as marking the beginning of the period of old age. According to Piersol (13) there are no diseases exclusively affecting the aged; there are certain changes which occur with such frequency in the aged that they can be considered as physiologic. These include graying of the hair; atrophy of the lymphoid tissues; the senile type of emphysema, with the resultant decrease in vital capacity; osteoporosis of the long bones and an increase in the size of the flat bones; arcus senilis; atrophy of the intervertebral discs, with resultant decrease in height; decrease in the papillary beds of the skin, causing a pallor which may be mistaken for anemia; general decrease in, or absence of, the deep tendon reflexes; and atrophy of the thyroid, liver, spleen, kidney, and all other organs except the heart.

The changes in the skin include an increased pigmentation of the exposed parts, a decrease in water and fat content, and a decrease of elasticity and growth and regenerative capacity. The ability of wounded tissues to heal is greatly retarded because of the decrease in the capacity for regeneration. Loss in elasticity seems to result from actual degeneration of the elastic connective tissue fibers, and perhaps partly from the decrease in the subcutaneous fat. A decreased secretion of the sebaceous glands may be responsible for the dryness of the skin in the aged. According to Carlson (3) the causes of the changes in structure and function in the human body with age are still obscure. Some may be the result of the genetic constitution of the individual or species, and some come about through the accidents of living—faulty diets, infections, over-work, laziness and gluttony. Heredity probably plays the primary role; however within a species, heredity is a factor in the life span of the individual and also even of the various organs within the individual, irrespective of environment, habits or disease. Nevertheless, it is practically impossible to separate the factors of aging from the effects of impairment due to accidents or disease. Davis (5) believes that the involutional processes which lead to senescence may be influenced by all factors which in any way modify cellular metabolism.

Senile pruritus is a common variety of generalized pruritus which is seen in persons of advanced age, and is probably a result of degenerative changes in the skin, with asso-

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ciated dryness and defective reparative powers. The diagnosis of senile pruritus must be differentiated from pruritus of the aged which has causes other then degenerative. The criteria for making a diagnosis of senile pruritus are not well founded. In our series of cases we made our diagnosis by a process of elimination and by the presence of certain degenerative changes. A generalized pruritus can be produced by a variety of conditions; hence, the diagnosis of "senile pruritus" is to be made only after other causes have been excluded. We considered the exciting cause of senile pruritus the atrophy of the entire thickness of the skin, including its appendages. The atrophy causes a thin, dry, irritable skin, and leads to generalized itching. A migratory, generalized pruritus, arteriosclerosis (arteriosclerotic changes can often be noticed in the retinal vessels long before they are noticeable elsewhere), arcus senilis, atrophic dry skin on exposed surfaces, and definite loss of elasticity were among the criteria required for diagnosis. Patients that had some other disturbances which are known to cause a generalized pruritus were not included in our series. The Kahn test, blood counts, and urinalysis were normal in all cases reported. The following conditions were eliminated as possibly responsible for or contributive to the pruritus: asteatosis, allergy, ingestion of drugs, functional disorders, skin eruptions, and skin infections such as scabies and pediculosis.

Feldman and others (7) believed that at least in some of the cases of senile pruritus the itching was caused by local or constitutional changes incidental to a sex hormone deficiency. They obtained good results from testosterone therapy in 12 out of 16 cases; the four remaining cases were improved.

Senile atrophy accompanied by senile pruritus is seen frequently in our dermatologic clinics at Grady Hospital (Emory University). This study was undertaken to evaluate the effectiveness of endocrine therapy, based on the concept that the aging process presupposes hormone deficiencies (Benjamin) (2). All our cases were males. The preparations used were testosterone propionate and methyl testosterone.[2] Testosterone propionate was given by injection and as an ointment, and tablets of methyl testosterone were given orally.

Hollander and Vogel (9) recently reviewed some of the pertinent literature on the value of testosterone in certain dermatoses and reported eight cases in which postclimacteric dermatoses in males was treated with testosterone propionate. They call attention to Reichert's (14) statement concerning the treatment of juvenile acne, senile pruritus, and senile eczema with endocrine preparations. The first report of the effects of androgen treatment was by Leipner (11). He reported five cases of dermatoses which improved by this treatment. The ineffectiveness of this therapy in 22 cases of acne vulgaris was reported by Molitch (12). The effect of androgenic substances upon pigmentation was studied by Hamilton and Hubert (8). Other dermatoses treated by testosterone were studied by Lafitte and Huret (10); and Edwards, Hamilton and Duntley (6). Riley (15) used testosterone propionate in 20 cases of acne vulgaris with irregular results. Promising results were noted by Cornbleet and Barnes (4) following intramuscular treatment of patients with acne vulgaris with testosterone propionate. Eight male patients having postclimacteric skin diseases were studied by Hollander and Vogel (9). They reported the effects of inunctions of testosterone propionate. Their results indicated amelioration of the symptoms. They concluded that in presenile and senile dermatoses this preparation is of definite value.

REPORT OF CASES

Case 1, S.B.M., an American male of Irish descent, aged 63, a manager of a freight concern, was first seen August 2, 1943. He had enjoyed comparatively good health until January of 1943 when his wife died and he began drinking heavily (2 quarts of liquor a day). Since May he suffered from a generalized pruritus which has been treated by local applica-

[2] The drugs, supplied through the courtesy of Roche-Organon, were *Neo-hombreol*, a form of testosterone propionate (10 mg. supplied in 1 cc. ampules for S.C. injections) *Neo-hombreol (M)*, a form of methyl testosterone, (10 mg. tablets for oral use), *Neo-hombreol*, a form of testosterone propionate, *(M)* (dosules, 4 mg., in an ointment base for local application).

tions of various antipruritic lotions with only temporary relief. In July he developed numerous boils. He was allowed only one pint of liquor daily by his physician. He was treated with large doses of vitamins by mouth and by injection. He also was given injections of stock vaccine, and the furunculosis gradually improved. Physical examination revealed several boils on the trunk. The skin of the entire body was dry and large plaques of erythema and scaling were present. Both extremities and the upper back were more severely involved and numerous excoriations on these areas could be seen. There was some follicular keratosis of the buttocks, outer thighs and upper arms suggestive of a vitamin A deficiency. The skin on the dorsum of both hands, on the neck and legs showed definite atrophy, loss of elasticity, and senile freckling. A few senile keratoses were present on the face. An early arcus senilis was present and early sclerosis of the retinal vessels was evident. Other physical and laboratory findings were normal. The prostate was normal. The patient continued to take vitamins by mouth, and in addition was given 100,000 units of vitamin A a day and crude liver extract intramuscularly three times a week. Locally oily, anti-pruritic lotions were used and fractional doses of roentgen rays were given at weekly intervals. The pruritus improved considerably after four weeks of treatment.

The patient did not return until January, 1944, at which time he had a severe recurrence of the pruritus, although the local and vitamin treatments were continued. At this time the liquor intake was decreased to one-half pint a day and he was also under the ministration of a physiotherapist. He was given ultra-violet therapy twice a week and several stronger anti-pruritic lotions were used. Two fractional doses of roentgen rays were again given at weekly intervals but all treatment gave only temporary relief. On November 3, 1944 the pruritus was so severe that we decided to try testosterone, and 10 mg. were given by subcutaneous injection. This was repeated at intervals of five days for four doses. The pruritus had improved considerably at the end of this time, and the injections were continued at weekly intervals for five weeks. The pruritus became more severe after this ninth injection, and the testosterone was given every third day for three injections. At this time the patient was completely free of the itching and was given an ointment containing testosterone to rub on his skin once daily. The pruritus was controlled until February 3, 1945 when methyl testosterone tablets were prescribed. One tablet was taken daily by mouth. Within three weeks the pruritus began recurring, and two weekly injections of testosterone were given to bring it under control. Since then he has returned once every three to four weeks for an injection of testosterone. This seems to be sufficient to control the pruritus. The prostate has remained normal. However, a leukoplakia of the tongue was first noticed in January, 1945. Although he was advised against smoking, he did not stop until recently, and the leukoplakia has increased in size. He consumed on the average more than one pack of cigarettes a day.

Case 2, W.H.C., an American, male contractor, aged 76, was first seen on January 4, 1945. A generalized, migratory pruritus had been present for several years. During the past year the pruritus has been progressively worse. Roentgen ray treatments gave some temporary relief. Starch baths, sedatives and local applications of various antipruritic salves also gave a temporary relief for a few hours each day. His health had always been good. Except for an appendectomy, he had had no serious illness. Most of his life was spent outdoors with plenty of exposure to sun. He drank liquor only occasionally, and smoked moderately. The skin on the entire body was dry, visibly thin, and atrophic, with considerable loss of elasticity. Senile freckling was present on the dorsum of the hands and on the face. A small squamous cell epithelioma, on the left ear, was removed. Arteriosclerosis was well advanced but he was mentally well preserved. An arcus senilis was present. Numerous excoriations were present, especially about the abdomen. Other physical findings were essentially normal. He had benign prostatic hypertrophy. The laboratory findings of the blood and urine were negative. He was given 10 mg. of testosterone by injection, and the pruritus improved immediately and practically cleared after the fourth injection. He was given testosterone ointment to rub on his skin once daily. After four weeks the pruritus began recurring slightly and the testosterone propionate has been continued at intervals of from three to four weeks. Only an occasional attack of itching occurs between the interval of each injection. The patient is still under treatment.

Case 3, D.O.J., a white, American, male, farmer, 81 years of age, was first seen October 31, 1942. This patient had pneumonia and malaria in the past without ill effects. In 1937 he was seen by a dermatologist who made the diagnosis of neurodermatitis, and during the same year he developed a generalized erythroderma with exfoliation. His skin has remained dry and itchy ever since, and roentgen ray treatments and local medications have given him only moderate and temporary relief.

Physical examination showed a well developed, elderly male, mentally alert and physically active for his age. The skin appeared very dry and scaly. There was a definite loss of elasticity and evident atrophy of the skin on the neck, anterior chest, dorsum of both hands, forearms and legs. Numerous excoriations scattered on the trunk and extremities were present. A well advanced arteriosclerosis and arcus senilis were present. There was some lichenification of the anterior scrotum. The prostate was normal. Other physical and laboratory findings were essentially normal. Testosterone was given by injection at intervals of five days, and considerable relief was noticed after the eighth injection. Two more injections were given at intervals of two weeks and

then four were given at intervals of four weeks. The patient was then given the hormonal ointment to rub into his skin for a period of one month. The pruritus was so much improved that the patient discontinued treatment from April until October 20, 1944, when he returned with a recurrence of his pruritus. Testosterone was again given at intervals of five days for six doses. The dose chosen at this time was 25 mg. The pruritus improved immediately after the first injection. A few days after the second injection the patient was completely relieved. Three more injections were given, although no symptoms were present. He was again given the hormonal ointment to rub into the skin daily. The patient has not returned since December, 1944.

Case 4, W.M.B., a white, male merchant, 80 years of age, was first seen on October 18, 1943. He had several serious illnesses but has enjoyed good health for the past several years, except for a migratory generalized itching. The itching and stinging never involved the whole body at one time although all parts of the body have been involved. He has always bathed frequently but was advised against this about six weeks prior to our examination. The discontinuance of baths did not seem to help the pruritus which remained the same. Various local applications have been used with temporary relief. Exposure to sunshine, contact with wool, and the drinking of beer seem to aggravate the itching. The skin appeared dry, scaly and inelastic. Numerous excoriations were present. The skin over the anterior surfaces of the legs was eczematized. The skin on the dorsum of the hands, upper chest and on the sides of the neck was atrophic; scattered senile keratoses were present on these areas. There were numerous seborrheic keratoses on the back. Arteriosclerois and arcus senilis were well advanced. There was a loss of deep tendon reflexes. He was not very alert mentally. He was constantly rubbing and scratching. A benign prostatic hypertrophy was present.

Testosterone was given subcutaneously at intervals of five days for ten doses before the pruritus was sufficiently controlled to give the patient noticeable relief. An ointment containing testosterone was prescribed to be rubbed in once daily. This was done for one month. There was no pruritus at the end of this time, but a complaint of stinging was still present. Methyl testosterone tablets were then prescribed in a dosage of 10 mg. three times daily. After one month the patient returned with a recurrence of his pruritus, and the ointment again was prescribed. At this time a squamous cell epithelioma was removed from the left cheek. This malignant change appeared in a senile keratosis. He was again seen on May 15, 1944. The ointment of testosterone was still being used. At this time a squamous cell epithelioma was removed from the dorsum of the right hand. Because of several senile keratoses present on the dorsum of the hands it was likely that the keratoses preceded the malignancy. The prostate was normal at this time. The pruritus was moderate and recurring. There was still some stinging of the skin, sufficient to be annoying. The hormonal ointment was discontinued, and testosterone propionate again was given by injection at weekly intervals. Six, weekly injections were given before the pruritus was again controlled. The subsequent injections were from three to six weeks apart, and seemed to be sufficient to control the itching. He would return whenever the itching would appear. One injection seemed to suffice for several weeks. This patient was lost from observation on November 13, 1944. At this time the prostate and general physical examination showed no change from our previous findings.

Case 5, L.W.C., a white, American, retired contractor, aged 72, was first seen on March 14, 1944. His chief complaint was a severe, generalized pruritus which has been getting progressively worse for three years. He has had various medical examinations but no reason for the pruritus was found. Local applications of various ointments and lotions would give him some temporary relief. His skin was dry, and scattered excoriations were present over the trunk and extremities. A scar was present on the left cheek where a skin cancer was removed several years previously. Numerous senile and seborrheic keratoses were present on the face. The skin on the face, neck, hands, and forearms showed definite atrophy and loss of elasticity. Arteriosclerosis was well pronounced, and the arcus senilis was very noticeable. The prostate was normal.

Testosterone was given by injection at five day intervals for five doses, without much relief. The injections were then given twice a week for five weeks, and, in addition, local inunctions of testosterone were used daily. The patient said he felt 50 per cent better at this time. The injections were continued at weekly intervals and the inunctions omitted. This was continued for five weeks. The condition remained about the same, and the injections were given at intervals of two weeks for three doses, and then at intervals of three weeks. The patient was given no treatment during July, and returned in August with a recurrence of his severe pruritus. Methyl testosterone was given three times daily by mouth, but after one month the pruritus and dryness of the skin were again as severe as on admission. On September 19th the patient again was started on testosterone by injection at five day intervals, and 20 mg. doses were used instead of the customary 10 mg. doses. The condition improved after six injections, but the patient became discouraged and discontinued his treatments.

Case 6, C.R.G., white, American male, age 68, was first seen on March 22, 1943. His chief complaint was a dry and itchy skin. The pruritus has been present off and on for ten years but has become severe during the past year. He has been diagnosed as having, and was treated for, seborrheic eczema and lichen planus. From March until August, 1942, he was given fractional doses of roentgen rays, crude liver extract by injection, stovarsol by mouth, and various anti-

pruritic emulsions, all without much benefit. His past health has been good except for the trouble with his skin.

When examined this patient was found to have an extremely dry and scaly skin. The back of the arms, hands and legs were erythematous, scaly and numerous excoriations were present. There was a definite loss of elasticity and senile freckling of the hands and face was present. Numerous senile keratoses were present on the face. Arteriosclerosis was well pronounced but the patient appeared mentally as well as physically alert. An arcus senilis was not very noticeable, and the prostate appeared normal. The laboratory findings were normal.

He was started on testosterone by injection at five day intervals. After seven injections he considered himself 60 or 70 per cent improved. The injections were continued until 20 injections had been given. The skin was clear at this time but moderate pruritus was still present; the patient believed himself more relieved than had ever been the case in the year in which the pruritus had become severe. Testosterone ointment was prescribed to be rubbed into the skin daily. After one month the patient called to report a recurrence of his pruritus. The inunctions were continued for two more weeks and in addition methyl testosterone tablets were given three times a day by mouth. Three weeks later, when he was seen at the office, the eruption and pruritus were almost as bad as when seen on his first visit. Further treatment was refused and the patient was not followed further.

Case 7, B.D., white, American farmer, aged 67, was first seen on January 4, 1944. A severe, generalized pruritus had been present for the past two years. The patient had an operation for gall stones in 1930, but otherwise enjoyed good health. He appeared to be normal physically and mentally. An arcus senilis and arteriosclerosis were present, though they were not advanced. The skin was dry and scaly and showed considerable loss of elasticity and senile atrophy. Numerous seborrheic warts were present on the back, and several senile keratoses were present on the face. The prostate was normal.

Testosterone was given by injection every five days for a total of ten injections, with very little relief. Testosterone by mouth and daily inunctions of testosterone were added to the therapy. Ten more injections were given but the response was not marked and the patient became dissatisfied. Locally antipruritic emulsions were used but with only temporary relief.

Case 8, B.M., a Turkish Jew, aged 72, was first seen in the dermatological clinic on January 4, 1944. His chief complaint at this time was a severe itching which was present for a period of 5 years and has been severe during the past several months. The pruritus would involve only parts of the body at any one time; however, all parts of the body have been involved at one time or another. He has been known as a hypertensive for at least ten years. In 1934 he was diagnosed as having chronic cardiovascular-renal disease with a blood pressure of 195/120. During the past two or three years he has had substernal pain brought on by exertion; relieved at first by rest; later by vasodilating drugs.

Physical examination showed the heart to be slightly increased in size. The rhythm was regular, but the quality of sounds was poor, and a systolic murmur was heard over the precordium. There was a severe sclerosis of the blood vessels. His blood pressure was 150/90. There was a benign prostatic hypertrophy. A marked decrease of deep reflexes was present. Other findings were normal. The skin was very dry, scaly and eczematized over the forearms and legs. There was loss of elasticity and some atrophy, most pronounced on the dorsum of the hands and neck. Numerous scattered excoriations were present on the body and some secondary infection was present. Symptomatic treatment with calamine emulsion and various anti-pruritics had been prescribed for several months in the medical clinic but only with temporary relief. It was decided to try testosterone propionate and a dose of 10 mg. was given at weekly intervals for seven weeks. At this time the patient was considerably improved and the texture of the skin seemed more normal. The dryness was considerably less and the eczematization of the hands and legs almost disappeared. Two injections were now given at intervals of two weeks, and two at intervals of three weeks. This seemed sufficient to control the pruritus. Methyl testosterone in doses of 10 mg. was given three times daily by mouth for six weeks at which time the patient reported that the pruritus had reappeared and was severe. An ointment of testosterone was prescribed and one dosule was rubbed in daily for two weeks. The pruritus improved at this time and the treatment was continued for six more weeks. The relief was great, but not as much as when the injections were used. The treatment was discontinued during the summer months. The pruritus persisted but was not severe. On October 11, 1944 the pruritus became severe again. After four weekly injections of testosterone the itching improved considerably, and one injection every three weeks thereafter seemed sufficient to keep the patient comfortable. On January 7, 1945 this patient died of cardiac failure.

Case 9, T.H., white American, aged 78, was first seen on February 10, 1943. This patient came to the hospital with an infected wound which was a result of "fighting" a few days previously. A generalized migratory pruritus was also a complaint at this time. The past history revealed meningitis and two attacks of pneumonia during childhood. Physical examination showed a man well preserved for his age of 78. He was mentally and physically alert. His blood pressure was 155/85. There were no abnormalities except for a slight decrease in the deep reflexes. The skin also was very dry and scaly and some atrophy and loss of elasticity was noticeable almost over the

entire body. An arcus senilis was present. Arteriosclerosis was present. He had an infected laceration of the right hand.

Symptomatic treatment was prescribed, giving temporary relief. The patient was seen periodically for one year. The itching became progressively worse, and in February, 1944, testosterone propionate was given at weekly intervals by injection. In six weeks the pruritus improved considerably, and the patient did not return until November 28, 1944. At this time the pruritus was severe again and he was given another injection. He would return at about monthly intervals for an injection. This would not control the pruritus completely, but sufficiently to keep him comfortable. Testosterone tablets were given to this patient but he refused to take them after one week, because they "did no good."

Case 10, S.B., a white American, aged 70, was first seen by us on July 7, 1942. He gave a history of itching and a skin eruption since 1930. He had been diagnosed as having pellagra, and had been treated in the past with brewers' yeast and dilute hydrochloric acid. He was hospitalized, and a gastric analysis showed no free hydrochloric acid and a decrease in the total acid content. There was a mild secondary anemia. The differential leucocyte count showed a mild eosinophilia. Other laboratory findings were normal. The patient also complained of weakness and diarrhea. A generalized dermatitis over the legs and feet was present; and there was a noticeable lichenification on the dorsum of the feet. A similar eruption was present on both hands and forearms, with a lichenification of the dorsum of both hands. A desquamation consisting of large flakes was marked on the legs and forearms. A mottled brown pigmentation was present on the areas involved and also on the scrotum. The face showed a similar pigmentation and thickening of the skin. Although the dermatitis was not marked, some atrophy of the papillae was noted. A diagnosis of pellagra was made.

He was given liver extract by injection and 100 mg. of nicotinic acid by mouth. There was not much improvement after two weeks and the patient was discharged. He continued treatment at home, taking nicotinic acid and brewers' yeast. His condition improved some after several weeks of treatment. His diet was inadequate due to social and economic circumstances. This patient was seen periodically until January, 1943. At this time the dermatitis was very severe. The skin over the entire body appeared dry and scaly. Marked arteriosclerosis was present. We decided to give testosterone by injection at weekly intervals. After six injections of testosterone, which was given in addition to the brewers' yeats, a marked improvement in the skin was evident. The pruritus also improved, although it did not subside. After ten weeks of treatment the dermatitis improved markedly and the patient felt better than he ever had since first seen in 1942. The patient failed to return for a follow up.

COMMENTS

It is our opinion that testosterone propionate is of definite value in the treatment of senile pruritus. Local applications of testosterone propionate are beneficial in some of these cases. In others no symptomatic improvement is obtained. Roentgen rays in subfractional and fractional doses may be used profitably, yet this treatment tends to aggravate the already dry skin. Recurrence of the pruritus limits the frequent use of roentgen therapy. In our series of cases oral methyl testosterone was found to be completely ineffectual. Methyl testosterone orally seems to be effective when the hormone is indicated and used in younger individuals, and this failure is not readily explained, although it may be due to a lower absorptive factor. Testosterone propionate by inunction was fairly successful in controlling the pruritus. From an economic standpoint, it is more advantageous to the patients. The hormone when given subcutaneously yielded the best result. After the pruritus was under control the treatment intervals were increased. An effective interval for injection in our cases was from three to four weeks. The subcutaneous implantation of testosterone pellets as recommended by Feldman *et al.* (7) will probably prove to be the treatment of choice in cases of senile pruritus which are resistant to symptomatic local treatment. Testosterone is contra-indicated in malignancy of the prostate. For this reason the prostate glands of all patients should be examined prior to and during the testosterone therapy.

The skin in some of our cases showed eczematization. Frequently the extensor surfaces of the forearms and legs and occasionally the face would have an appearance of a subacute dermatitis. In several cases these areas would show an early lichenification of the skin which apparently was caused by friction and rubbing of the areas involved. With an improvement of the pruritus the skin manifestations would also improve and eventually clear up. In some cases the erythema was pronounced and a localized edema was present. The first impression was that of a contact dermatitis. However, this dermati-

tis, as a rule, was resistant to local symptomatic treatment.

The dryness of the skin seemed to be less pronounced while the patients were under treatment. This clinical observation would support the findings of Rony and Zakon (16). In their report six prepubertal boys received testosterone propionate parenterally for two weeks. Biopsies from the pubic region made just before and two or three days after treatment showed decided increase in number and size of sebaceous glands in all subjects, which the authors consider direct evidence of a stimulating action of androgen on the sebaceous glands in man.

Several of our cases merit special comment:

Case 1, S.B.M. The condition was apparently senile pruritus in an alcoholic. The pruritus and dermatitis were controlled by testosterone when vitamins orally failed to improve the patient's skin condition. It was interesting to find that the dryness and accompanying dermatitis and eczematization improve along with the relief of the pruritus. There is apparent stimulation of the inactive sebaceous glands which function again under testosterone therapy.

Case 3, D.O.J. In the beginning, eight injections of testosterone were given subcutaneously in 10 mg. doses before the pruritus was sufficiently relieved. When the testosterone was discontinued the pruritus recurred. The testosterone was given in 25 mg. doses and the response was immediate. It seems likely that 10 mg. dosages of testosterone are rather small and larger doses should be given in order to give the patient early relief. In none of our cases did the testosterone therapy stimulate any sexual feelings at any time during the course of treatment.

Case 10, S.B. Although pellagra was present, the skin changes were not responsive to liver and nicotinic acid until testosterone was used. A combination of pellagra and senile pruritus apparently was present.

SUMMARY

Ten patients having senile pruritus were treated by local applications and parenteral injections of testosterone propionate and by oral methyl testosterone. Only those cases that had failed to respond after other prolonged symptomatic measures were chosen. Seven patients responded favorably; two improved; and one failed to show any alleviation of the condition. Testosterone propionate given by injection and by inunction was of great value. No improvement was obtained with oral methyl testosterone.

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The Reliability of the Aschheim-Zondek Test in Pregnancy

(A report of two thousand routine tests)

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THE PROCEDURE introduced by Aschheim and Zondek has proven to be very reliable for the detection of early pregnancy, as well as for the differentiation of pregnancy from hydatidiform moles and chorionepitheliomas. Many modifications have been introduced in the procedure, primarily in the quantity of urine, and the time and number of injections. These changes are immaterial, since the majority of publications show that regardless of the modifications, this test has proven to be highly accurate. The accuracy of the test has been repeatedly reported to be between 98 and 99 per cent.

Allen and Dickens (1930) (1) have emphasized the importance of performing the test on young mice. They state that the age of the mice should not exceed 24 days. These authors found that corpora lutea are usually found to be accompanied by corpora hemorrhagica. Corpora lutea were present without corpora hemorrhagica in only four of their 126 positive tests.

This report is an analysis of 2000 consecutive routine qualitative pregnancy tests performed on mice, at the Naval Medical School during a seven months' period (November, 1944, to June, 1945). Six hundred and fourteen of these specimens were received by mail delivery from various areas of this country—from as far north as Connecticut to the southern area of Florida, and as far west as Oklahoma. The majority of these specimens were from two to four days in transit. Very few contained any preservative. The other 1386 specimens were received by messenger, the day procured.

THE TECHNIQUE OF THE TEST AS USED AT THE NAVAL MEDICAL SCHOOL

The Endocrinology Laboratory requests that the clinician send either the first voided urine specimen, having a specific gravity of at least 1.015, or a specimen of serum.

All urine specimens received by mail are detoxified (shaking one part of urine with approximately three parts of ether) before being injected into the test animals. Four immature female mice, three to six weeks old, are routinely used for the test; however, during a period of scarcity of mice, three mice were used in 467 of these reported tests. The mice used for this study were not carefully bred or selected. The majority of these animals were obtained from four commercial breeders.

Each mouse is injected subcutaneously under the loose skin of the back, once daily for three successive days, with 0.25 cc. of urine or serum. On the morning of the fifth

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[1] The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

day (approximately 90 to 96 hours after the initial injection), the mice are asphyxiated with illuminating gas, then secured with pins to large animal boards and opened. The number of corpora hemorrhagica and corpora lutea are counted on each ovary of all mice. The test is reported positive if one or more hemorrhagic follicles, or a definite corpus luteum is present on any one of the animals in the set. If the presence of a follicle is questionable the test is reported as doubtful and another specimen is requested. In the absence of both corpora hemorrhagica and corpora lutea, the test is reported as negative. The clinician is requested to forward his final conclusions on each patient, in order that the laboratory can determine the accuracy of the tests.[2]

RESULTS

In this series, 118 of the tests were performed on serum and 1882 on urine. The results reported to the clinician are listed in Table 1. Positive tests were obtained on approximately 75 per cent of the serum specimens and approximately 70 per cent of the urine specimens.

TABLE 1. RESULTS OF TWO THOUSAND ASCHHEIM-ZONDEK TESTS

Type of specimen	Results obtained			Total
	Positive	Doubtful	Negative	
Urine	1310	83	489	1882
Serum	88	4	26	118
Total	1398	87	515	2000

The accuracy of the Aschheim-Zondek test is demonstrated in Table 2. Only 844 of the 2000 reports were returned to the laboratory with final clinical conclusions. Four of the 629 reported positive specimens were from non-pregnant women; whereas five of the 190 reported negative specimens were from pregnant women. These five patients did not have early pregnancies and positive results should have been obtained. Therefore, these five false negative reports are considered as errors. Sixteen of the negative reports were on specimens obtained from women in early pregnancy; two were specimens taken six days after the first missed menstrual period.

TABLE 2. ACCURACY OF THE ASCHHEIM-ZONDEK TEST
(Results of eight hundred and nineteen cases)

Results of test	Confirmed by clinical evidence	Very early pregnancies	Errors	Total tests
Positive	625		4	629
Negative	169	16	5	190

[2] The Endocrinology Laboratory of the Naval Medical School also performs Friedman Tests and "Frog Tests."

POSITIVE TESTS ON NON-PREGNANT PATIENTS (FALSE POSITIVE REPORTS)

Case #1: The urine specimen was received by mail delivery. The test was negative. Before this test was completed, a second specimen dated three days later than the first specimen was received and the second test was positive. The final report states that this patient menstruates regularly and no clinical basis for pregnancy was found.

Case #2: This urine was received by messenger on November 30th. The test was positive. The clinician did not believe the patient to be pregnant, and the test was repeated and again found to be positive on the second specimen, December 6th. A third test on urine, December 14th, was negative. The test on serum on December 20th was also negative. This patient was not pregnant.

Case #3: The test on this urine was reported as positive. The clinician later reported that there was no evidence of pregnancy.

Case #4: This test on urine was reported positive. Repeated clinical examinations showed no evidence of pregnancy.

NEGATIVE TESTS ON PREGNANT PATIENTS (FALSE NEGATIVE REPORTS)

Case #1: This test was reported negative; seven days later a repeated test was positive. All signs of pregnancy were present. An x-ray showed a fetus of approximately five months' development.

Case #2: The first test was doubtful. A repeated test 14 days later was negative. A third test 41 days after the first test was

negative. An x-ray taken one month after the third test showed a fetus of approximately 18 weeks. All clinical signs of pregnancy were present.

Case #3: A urine specimen from a patient suspected of having an ectopic pregnancy gave a negative test.

Case #4: Two tests with a ten day interval intervening were negative. The second test was performed on a catheterized specimen. The clinician reported the presence of the fetal heart beat.

Case #5: A test reported as doubtful was repeated and reported as negative. A repeated clinical examination proved this patient was pregnant.

PATIENTS WITH EARLY PREGNANCY

Sixteen patients, of whom nine did not state the date of the last menstrual period, gave negative results in the first test and positive results on repeated tests. The clinicians reported these nine patients as having very early pregnancies. (Both tests on one of these nine patients were made on serum.) The quantity of hormone present in the first specimen from each of these 16 patients apparently was insufficient to obtain positive results.

TABLE 3. REPEATED TESTS, CASES OF EARLY PREGNANCY

Days after last menstrual period		
First test		Repeated tests positive
Negative	Doubtful	
34		45
35		46
	35	47
37		50
38		53
40		54
41		54
	47	55

Table 3 demonstrates that there is a variation in the quantity of the hormone excreted. In some individuals the quantity of hormone present is sufficient to produce a positive test earlier in pregnancy than in others. Kurzrok in 1932 (2) obtained a positive test one day after the missed period. One of the patients in this series gave a positive test three days after the first missed menstrual period.

TABLE 4. PERCENTAGE OF MICE REACTING TO THE HORMONE[3] (When four mice were autopsied)

Number of tests performed	Number of mice	
	Reacting	Not reacting
303 tests	4 mice (100%)	All mice reacted
306	3 (75%)	1 mouse (25%)
95	2 (50%)	2 mice (50%)
96	1 mouse (25%)	3 (75%)
When three mice were autopsied		
187	3 mice (100%)	All mice reacted
176	2 (68%)	1 mouse (33%)
81	1 mouse (33%)	2 mice (68%)

[3] This includes tests on serum and urine.

PERCENTAGE OF MICE REACTING TO THE HORMONE

It well known that some mice will not react satisfactorily to the hormone present in the urine or serum. In 1344 positive tests, when at least three mice were still living on the morning of the fifth day, 1322 (26.8%) of the 4932 mice did not react; that is, no corpus luteum or hermorrhagic follicle was present on either ovary (Table 4).

COMPARISON OF REACTIONS IN MICE

Positive reactions were recorded as one, two, three and four plus; depending on the number of follicles and the number of ovaries reacting. Analysis of the results show that approximately 70 per cent of the positive specimens produced moderate reactions. Only five to seven per cent produced very marked reactions. There was no marked difference in degree of reaction between urine and serum (Table 5).

TABLE 5. COMPARISON OF THE INTENSITY OF REACTIONS IN MICE

Type specimen	Intensity of reaction			
	4 plus	3 plus	2 plus	1 plus
Urine	69 tests	235 tests	450 tests	556 tests
Serum	6	18	24	40
Total	75	253	474	596

TABLE 6. COMPARISON OF REACTION TO AGE OF MICE
(Showing results obtained in testing 664 positive specimens)

	Approximate age of mice in days[4]						
	21	24	28	30	32	35	42 days
Number of mice in age groups	54	134	278	325	372	513	373
Number of negative mice	24	32	65	74	86	141	124
Per cent of negative mice	44	24	23	23	23	27	33
Total corpora hemorrhagica	73	317	676	824	973	1290	862
Average hemorrhagic follicles per mouse	2.42	3.14	3.17	3.28	3.40	3.47	3.46
Total corpora lutea	235	800	1865	2486	3447	5531	3699
Average corpora lutea per mouse	7.83	7.93	8.75	9.90	12.05	14.89	14.89

[4] At time of initial injection.

COMPARISON OF AGE OF MICE

As previously stated in this report, the statement has been published that the age of the mice should not exceed 24 days. Therefore, in 1000 tests the approximate age of the mice was determined and recorded. (Due to a scarcity of mice, all available immature female mice were used.) Only results obtained on mice injected with positive specimens were used in the computation of Table 6. These results show that a very high percentage of the young mice (21 day old group) did not react. The lowest percentage of negative reactions occurred in mice in the 28, 30 and 32 day old groups. The average number of hemorrhagic follicles and corpora lutea increased with the age of the animal.

SPECIFIC GRAVITY IN RELATIONSHIP TO REACTION

There appears to be no marked relationship to the specific gravity of the urine specimen and the degree of reaction (Table 7).

In this series of 1401 doubtful and positive urine specimens, the lowest specific gravity recorded was 1.003 and the highest was 1.040. There were five specimens with a specific gravity less than 1.007, on which positive results were obtained. The majority of the specimens (80 to 83 per cent) of each group had a specific gravity between 1.015 and 1.030.

THE STABILITY OF THE HORMONE

As previously stated, some of the specimens were received by mail delivery two to six days after voiding. Very few of the specimens contained any preservative. Since the results of these tests appeared satisfactory, there is no reason to believe that the hormone deteriorated in transit. To further check the stability of the hormone, three specimens of urine giving a three plus reaction were divided into two portions. One portion of each specimen was stored in a refrigerator at (8 to 10° C.), and the other portion was kept at room temperature (20 to 30° C.). After 18 days of storage, all specimens were retested. The specimens stored at room temperature deteriorated much more than those stored in the refrigerator (Table 8).

MORTALITY OF MICE DURING THE TEST

Various investigators have reported a very high mortality in the mice used for pregnancy

TABLE 7. COMPARISON OF SPECIFIC GRAVITY TO DEGREE OF REACTION

Specific gravity of specimen	Degree of reaction				
	Doubtful	1 plus	2 plus	3 plus	4 plus
Number of specimen less than 1.015	8	34	23	22	3
Between 1.015–1.030	71	461	373	186	54
Between 1.031–1.035	7	56	49	24	11
Over 1.035	1	6	9	3	0
Total number of specimens in group	87	557	454	235	68
Average specific gravity of group	1.0222	1.0234	1.0236	1.0234	1.0231

tests. Ehrhardt (3) stated in 1931 that the mortality may be as high as 20 per cent.

In this study, all urine specimens received by mail delivery were detoxified before being injected into the mice. The mice of each set were kept in glass jars, covered with perforated metal tops. In this series of 2000 tests, 7360 mice were used, of which 135 died after the first injection (1.834%). During the last week of July and the first part of August 686 mice were injected with routine specimens, of which 13 died (1.89%).

TABLE 8. STABILITY OF THE HORMONE
(Storage at room and refrigerator temperature)

Specimen	Original test	After 18 days storage	
		Refrigerator (8–10° C.)	Room temperature
#1	3 plus	3 plus	1 plus
#2	3 plus	2 plus	1 plus
#3	3 plus	1 plus	negative

The following procedure is used at the Naval Medical School for detoxification of urine specimens:

(1) If the specimen is alkaline, it is acidified with 10% acetic acid (avoiding excess acid).

(2) Approximately 90 cc. of ether is added to approximately 30 cc. of urine in a separatory funnel. This mixture is shaken for about five minutes.

(3) The two fluids are allowed to separate, by standing two or three minutes. The bottom layer of urine is carefully drawn off into a wide shallow dish, allowing a small quantity of urine to remain in the separatory funnel. The remaining traces of ether are removed by evaporation, with the aid of an electric fan.

(4) Approximately 1 gm. of glucose is added to the detoxified specimen.

SUMMARY

(1) The Aschheim-Zondek Test is unquestionably a very reliable test for the detection of pregnancy. There were four errors (0.6%) in 629 specimens from pregnant women. There were five errors in 174 specimens from non-pregnant women.

(2) Some women may excrete a sufficient quantity of hormone to give a positive test very early in pregnancy. In this study a positive test was obtained on a urine three days after the missed menstrual period. In seven instances, when the first specimen was tested less than two weeks after the missed period, the tests were negative. Repeated tests were positive.

(3) Approximately 25 per cent of immature mice will not react to the hormone.

(4) Mice react equally as well to serum as they do to urine from pregnant women.

(5) The ideal age of mice for pregnancy tests was found to be between 25 and 32 days. A greater percentage of mice in this age group will react to a positive specimen. However, more hemorrhagic follicles and corpora lutea are found in older mice.

(6) The mortality of mice in this investigation was less than two per cent.

ACKNOWLEDGMENTS

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Thiouracil Derivatives of Greater Activity for the Treatment of Hyperthyroidism[1]

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A continued investigation of compounds which inhibit the function of the thyroid gland has revealed that appropriate substituents on the thiouracil molecule confer a greatly increased activity. The compounds 6-ethylthiouracil and 6-*n* propylthiouracil are among a group which are approximately ten times as active as thiouracil when tested in rats; compounds of this class have exhibited an activity far superior to any of some 300 thus far explored (2). Tests in rats have also shown that these derivatives exert a more lasting effect following a single dose than does thiouracil, a substance known to be rapidly eliminated from the body. These derivatives have the further therapeutic advantage of a greater activity-toxicity ratio; while they are more toxic than thiouracil on a weight basis they are considerably less toxic in acute and in chronic experiments when administered in quantities calculated on the basis of equivalent anti-thyroid effect. A selected group of the more effective anti-thyroid compounds when tested in chicks likewise showed that these thiouracils were much more active than any other compounds hitherto investigated (6).

In view of these considerations it seemed fitting to test the effectiveness of ethylthiouracil and propylthiouracil in human beings suffering from hyperthyroidism. The small doses which have proved to be effective and the favorable results which have been observed show that these compounds are well suited to clinical use.

OBSERVATIONS

The first clinical tests were made with ethylthiouracil. It was administered to fourteen patients in doses of from 20 to 100 mg. daily with the aim of determining the minimal dosage which would be uniformly effective. This limited trial revealed a high order of activity, but observations on this compound were not extended further for two reasons: it proved to be a difficult substance to synthesize, and animal tests subsequently revealed the propyl derivative to be somewhat superior both as to its antithyroid potency and as to its more prolonged action following a single dose. Subsequent observations were therefore confined to propylthiouracil administered in the form of tablets containing 25 mg. each, given by mouth at intervals of 8, 12 or 24 hours.

The pertinent clinical data on these two

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[1] The thiouracil derivatives recently synthesized by Roblin and coworkers [Anderson, G. W., Halverstadt, I. F., Miller, W. H., and Roblin, R. O. Jr., Studies on chemotherapy. *X* Antithyroid compounds. 5- and 6- substituted 2-thiouracils, *J. Am. Chem. Soc.* (in press)], were made available for testing by Dr. Roblin and his associates of the American Cyanamid Company, Stamford, Conn. Tablets of 6-*n*-propylthiouracil were supplied by Dr. S. W. Hardy of the Lederle Laboratories, Inc., Pearl River, N. Y.

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compounds are summarized in Table 1. The 14 patients treated with ethylthiouracil received the compound for periods of from one to seven months; subsequently the treatment of eight of these patients was continued with the propyl derivative. In 29 instances propylthiouracil alone was used, and thus its effectiveness was observed in a total of 37 cases. For a period of two weeks one patient received isopropylthiouracil, a compound very similar in its properties to the ethyl derivative.

Most of the patients were unquestionable examples of Graves' disease; this diagnosis remained unestablished in *Cases 1, 3, 6,* and *12.* The diagnosis of hyperthyroidism with nodular or adenomatous goiter was made in *Case 15.* One or more thyroidectomies had previously been sustained by *Patients 3, 11, 26, 27, 31, 39,* and *42.*

The methods of study and general management of the patients were similar to that used in former studies on thiouracil and thiobarbital (3, 4). Eleven patients were under observation in the hospital when treatment was instituted; the others were ambulatory throughout. The only supplementary vitamins given were those which were prescribed during hospitalization as a part of hospital routine. The various accessory food factors which have been claimed to influence drug toxicities were purposely avoided in order not to complicate the comparison between these and earlier compounds.

Iodine therapy had been recently discontinued in 13 instances, and failure to respond promptly was attributed to this factor in *Patients 9, 10, 20, 24, 32* and *39;* in *Patients 26* and *27* there was no delay in response.

The recovery of the patients so treated suffering from hyperthyroidism was similar in every regard to the familiar response to thiouracil. There were no significant variations in the relative rates of improvement of the several symptoms, signs, and laboratory evidences of the disease from the pattern commonly observed with thiouracil. It is notable, however, that there was no instance of any of the serious reactions which sometimes complicate thiouracil therapy.

The potency of these two antithyroid compounds is well illustrated by the rate of recovery following their administration in small doses. For example, 50 mg. daily of ethylthiouracil in *Case 5* brought about symptomatic improvement in four days; in ten days reversion to normal rhythm of the associated auricular fibrillation occurred. The symptomatic recovery in *Case 14* was equally rapid with 75 mg. daily. Propylthiouracil in a dose of 25 mg. once daily brought about a prompt relief of symptoms in *Case 22;* the basal metabolic rate fell from +43 per cent to +18 per cent, and the body weight increased from 40.9 to 47.3 kgm. (90 to 104 pounds) in 18 days. A weight gain of 8.6 kgm. (19 pounds) occurred in *Patient 29* during the first 24 days of treatment with 50 mg. of propylthiouracil daily. Further convincing evidence of the antithyroid effectiveness of both substances was provided by the complete recovery of five of the six cases of thyrotoxic heart disease. *Patient 9* had previously received iodine and had not responded satisfactorily before the treatment was changed to thiouracil. The other five patients experienced a complete restoration of normal cardiac function.

DOSAGE

One of the most difficult features in this type of investigation is the determination of the minimal dose of a compound for initial therapy which will be adequate in all cases to induce a prompt response. One manifestation of this difficulty is to be observed in the many publications on the use of thiouracil wherein one observes that scant attention has been given to the matter; as a consequence very little new information concerning the optimal dose of thiouracil which should be used during the early weeks of treatment has come to light. During the clinical trials with thiobarbital nearly a year passed before it was suspected that the dosages being used were excessive. This error was fostered by too strict a comparison between the experimental animal and man; thiobarbital had proved to be approximately

TABLE 1

Patient no.	Age & sex	Initial body weight (kgm.)	Dosage mg. (*days*)[2]	Additional diagnoses[3] and previous treatment	Response
6-Ethylthiouracil					
1	35F	82.0	75(*33*)100(*14*)50(*14*)20(*35*)40(*49*)0(*28*)100(*42*)	Anxiety state; ? hyperthyroidism.	BMR fell; anxiety state unchanged.
2	61F	56.8	50(*30*)0(*281+*)	Initial response to thiobarbital good. (Ref. 4, *Case 12.*)	Response continued; remained well 11 mos. without treatment.
3	50F	54.0	50(*20*)30(*42*)50(*49*)100(*110*)	Thyroidectomy 1925; rheumatic heart disease with failure; ? hyperthyroidism.	BMR fell; goiter developed; heart failure not improved.
4	28F	50.4	50(*54*)20(*54*)50(*112*)	Partial response to thiobarbital. (Ref. 4, *Case 9.*)	Continued response.
5	60F	46.8	50(*5*)0(*2*)20(*30*)30(*21*)50(*49*)75(*56*)	Previous toxic reactions to thiobarbital and sulfadiazine. (Ref. 4, *Case 4.*)	Auricular fibrillation reverted in 10 days.
6	54F	49.5	30(*19*)60(*3*)30(*8*)60(*47*)	? Hyperthyroidism.	BMR fell with 60 mg.; no symptomatic improvement.
7	30F	59.0	30(*14*)0(*4*)50(*119*)0(*5*)		None to 30 mg.; prompt response to 50 mg.
8	38F	73.1	60(*18*)0(*4*)75(*119*)	Thyrotoxic heart disease.	Slow response until dosage increased.
9	62M	82.7	75(*71*) [Thiouracil 400(*160+*)]	Iodine; thyrotoxic heart disease.	Delayed effect; responded to thiouracil; heart improved.
10	55M	53.1	75(*20*) [Thiouracil 300(*47*)]50(*60*)	Iodine; thyrotoxic heart disease.	No response in 20 days; good control after thiouracil; heart normal.
11	68F	44.0	100(*42*)0(*2*)100(*1*)	Thyroidectomy 1941.	Good response; urticaria; controlled by 0.4 gm. thiourea daily.
12	35F	54.5	100(*60*)	Anxiety state; cirrhosis of the liver.	No effect (Not thyrotoxic).
13	35F	48.1	100(*32*)	Pregnancy.	Satisfactory response.
14	52F	50.0	75(*60*)0(*10*)	Thiouracil 11 mo. Remission, 4 mo.; iodine 5 mo. (Ref. 3, *Case 8.*)	Symptoms controlled in 4 days.
6-n-Propylthiouracil					
1	—	—	50(*45*)25(*125+*)	Ethylthiouracil.	Goiter developed with 50 mg. daily.
4	—	—	25(*28*)0(*154+*)	Ethylthiouracil.	Sustained remission, 5 mo. without treatment.
5	—	—	50(*43*)0(*4*)25(*102*)0(*30*)	Ethylthiouracil.	25 mg. daily adequate for maintenance.
7	—	—	50(*116*)0(*60+*)	Ethylthiouracil.	Remained well with 50 mg.; sustained remission.
8	—	—	50(*122*)0(*60+*)	Ethylthiouracil.	Well maintained; complete recovery.
10	—	—	50(*152+*)	Ethylthiouracil.	Early myxedema with 50 mg. daily.
13	—	—	50(*131*)25(*54*)	Ethylthiouracil.	Well controlled; pregnancy uncomplicated.
14	—	—	75(*122+*)	Ethylthiouracil.	Well controlled.
15	51M	60.0	50(*14*)	Toxic adenoma.	Prompt; hyperthyroidism returned when treatment was discontinued; adenoma removed.
16	37F	47.7	50(*25*)75(*49*)50(*103*)0	Thyrotoxic heart disease.	Prompt; all cardiac manifestations disappeared.
17	64F	48.1	50(*184+*)		Prompt fall in BMR.
18	49F	63.6	75(*7*)50(*140+*)	Thyrotoxic heart disease.	Symptoms controlled in 6 days.
19	41F	53.1	75(*50*)150(*63*)75(*43+*)		Somewhat delayed; 75 mg. possibly inadequate.
20	60F	47.7	75(*32*)150(*63*)75(*36+*)	Iodine 3 wks.	Delayed response.
21	48F	50.0	75(*14*)	Thiouracil several times; febrile reaction.	Marked effect in two weeks; thyroidectomy.
22	45F	40.9	25(*153+*)	Fever and leukopenia from thiouracil and thiobarbital. (Ref. 4, *Case 13.*)	Completely controlled by 25 mg. daily.
23	39M	63.6	75(*118+*)		Prompt.
24	27F	54.5	75(*53*)0(*14*)75(*50+*)	Iodine.	Delayed; recurrence when discontinued; second response prompt.

TABLE 1—*Continued*

Patient no.	Age & sex	Initial body weight (kgm.)	Dosage mg. (*days*)[2]	Additional diagnoses[3] and previous treatment	Response
6-n-Propylthiouracil—Continued					
25	55M	56.3	75(*80*)150(*7*)75(*20*+)	Iodine; thyrotoxic myopathy; auricular fibrillation.	Moderately rapid; normal cardiac rhythm in 3 wk.; complete response delayed.
26	35M	78.1	50(*114*+)	Thyroidectomy 1943; febrile reaction to sulfadiazine and thiouracil. (Ref. 1.)	Prompt—no evidence of toxicity.
27	54F	65.4	75(*14*)50(*104*+)	Thyroidectomy 1928; iodine 2 weeks.	Prompt despite previous iodine.
28	56F	52.2	50(*93*+)	Rheumatic heart disease.	Marked improvement in 4 weeks.
29	50F	67.2	50(*91*+)	Good response to thiouracil; remission 18 mo. without treatment. (Ref. 3, *Case 5.*)	Prompt—8.6 kgm. weight gain in first 24 days.
30	53F	44.0	75(*14*)50(*75*+)		Immediate improvement; further recovery slow with 50 mg.
31	48F	82.0	50(*46*)75(*36*)50	Thyroidectomy 1943; severe exophthalmos.	Hyperthyroidism controlled; eyes unimproved.
32	53M	79.5	75(*74*+)	Heart failure; iodine 1 year.	Delayed.
33	60M	65.4	75(*62*+)	Peripheral vascular disease of legs; ophthalmoplegia; iodine 18 mo.; none 5 wk.	Prompt control of hyperthyroidism; eyes unchanged.
34	27F	49.5	75(*65*+)	Pregnancy; iodine 3 mo.	Slightly delayed.
35	45F	49.5	75(*51*+)	Two thyroidectomies.	Prompt.
36	26F	56.3	75(*61*)50	Pregnancy.	Rapid.
37	37F	52.2	75(*52*+)	Anxiety neurosis.	
38	45M	61.8	75(*46*+)	Anxiety neurosis; iodine 10 days.	Response began third week.
39	39F	52.7	75(*26*+)	Thyroidectomy 1939; iodine 15 mo.	Moderately delayed.
40	76F	41.8	75(*28*+)	Iodine several years; x-Ray treatment 1942.	Delayed.
41	44F	82.7	75(*26*+)		
42	44F	61.8	75(*24*+)	Thyroidectomy	Prompt.
43	49F	55.4	75(*22*+)		Moderately rapid.

[2] The dosages are expressed in mg. per day and the italicized figures in parentheses signify the number of days that dose was administered.

[3] The diagnosis in all cases was uncomplicated hyperthyroidism unless otherwise indicated.

1.7 times as active as thiouracil in the rat (2, 5) whereas it later was clear that it is three or four times as active as thiouracil in man (4). In the cases of ethyl- and propylthiouracil the animal tests showed a potency about tenfold that of thiouracil and if this ratio were to hold for man the initial dose should be about 40 mg. per day.

The data shown in Table 1 indicate that this estimate is a little too low. During the earlier trials the dosage of ethylthiouracil was changed frequently in order to establish a rough estimate of the required dosage. While some of the cases proved unsatisfactory for this purpose a fairly good approximation could be made. For example 50 mg. was adequate in *Patients 4* and *5* while 20 mg. was not. *Patient 7* continued to lose weight and to show a rising basal metabolic rate with 30 mg. daily but recovered rapidly when the dose was increased to 50 mg. *Patient 8* responded definitely to 60 mg. daily but the rate of improvement was slow until the dosage was increased to 75 mg. daily. These limited data indicate that the initial dose of ethylthiouracil should be about 75 mg. daily.

In view of these considerations propylthiouracil was usually given in a dose of 75 mg. daily. In several instances the rate of the response seemed unduly slow, and for this reason *Patients 19*, *20* and *25* received 150 mg. daily for a short period of time and this larger dose seemed to accelerate the rate of recovery in one instance (*Patient 20*). It is debatable whether the larger dose was

essential, for quite satisfactory control of hyperthyroidism occurred in the other 18 patients given 75 mg. daily, in the four, given 50 mg. daily and even in the one, given only 25 mg. daily. While these observations permit a more accurate estimate of the proper dose of propylthiouracil than was possible in the case of the ethyl derivative the values 50 or 75 mg. daily must be considered as approximations only. It would seem that a dose of 25 mg. at eight-hour intervals while uniformly effective is probably not excessive. This conclusion is supported by the observation that myxedema has seldom occurred with maintenance doses of 25 or 50 mg. daily.

The estimation of the maintenance dose provides a useful index of the relative clinical effectiveness of antithyroid compounds. An inadequate dose permits hyperthyroidism to return; should excessive doses be continuously administered manifestations of myxedema ensue and the thyroid gland begins to enlarge.

The maintenance dose of these new thiouracil derivatives would appear to be 25 to 50 mg. daily or about one third to two thirds of the initial dose. Thus far there has not been an instance when these maintenance doses seemed too small and only in a few instances have they appeared to be too large. *Patient 1* developed a striking thyroid enlargement during the eighth month of treatment while receiving 25 mg. of propylthiouracil twice daily. The thyroid continued to enlarge and to become more vascular when the dose was reduced to 25 mg. daily. *Patient 3* was similarly affected during the 4th month of treatment by 50 mg. of ethylthiouracil twice daily and *Patient 10* exhibited signs of myxedema while receiving 50 mg. daily of propylthiouracil. An adequate maintenance dose of propylthiouracil proved to be 25 mg. daily in four instances. An interpretation of such a minimal maintenance dose is complicated, however, by the fact that the majority of patients undergo a complete remission sometime during the maintenance period, and no longer need any therapy whatever. Were this not recognized a very small dose might be credited as responsible for continued health. The data at hand would, however, allow the preliminary estimate that the proper daily maintenance dose should be within the limits of 25 to 50 mg.

This value, together with the estimate of the optimal initial dose, indicates that propylthiouracil (and probably also ethylthiouracil) is distinctly more active in man than thiobarbital and roughly five times as effective, on a weight basis, as thiouracil.

POSSIBLE SIDE EFFECTS

In this series of cases there occurred only one untoward reaction. In no other instance were any unpleasant subjective sensations noted as a result of therapy. This reaction occurred in *Case 11;* after 42 days of treatment with 100 mg. daily of ethylthiouracil there developed a generalized pruritus. Accompanying the irritation from scratching, or perhaps because of it, there appeared an urticarial eruption on the body and extremities. The disturbance cleared after the drug was discontinued only to reappear when treatment was resumed. A similar reaction followed the subsequent administration of thiouracil and a much milder reaction from thiourea. Nevertheless, continued treatment with thiourea was possible without discomfort. This patient had on previous occasions developed "hives" from the eating of certain fruits. A subsequent test with ethylthiouracil was not made. None of the 37 patients treated with propylthiouracil has experienced any untoward reaction.[4]

More significant than the low incidence of side effects was the observation that these compounds were tolerated by patients who had previously reacted unfavorably to the administration of thiouracil or thiobarbital. *Patient 5* had previously been seen to experience four severe drug reactions; on two occasions there developed a febrile reaction during the administration of thiobarbital as previously reported (ref. 4, *Case 4*) and the

[4] Since this report was written 15 additional patients have been treated with propylthiouracil. Thus this compound has been given to a total of 52 individuals in therapeutic dosages and no side effects have been noted.

patient had twice reacted with fever and an extensive skin rash from sulfadiazine therapy prescribed for recurrent acute pharyngitis. Ethyl- and later propylthiouracil were given to control the recurrent hyperthyroidism, but in view of the earlier reactions this was done with some apprehension. The disease was rapidly controlled and no evidence of sensitivity to either compound was manifest during 11 months of treatment. *Patient 21* had been treated in another country with thiouracil in an intermittent and seemingly unsatisfactory manner. After thiouracil had been discontinued and readministered several times a febrile reaction occurred; treatment was stopped, and a state of hyperthyroidism returned. Prompt control of the severe hyperthyroidism followed when propylthiouracil was given in a dose of 75 mg. daily; there was no untoward reaction of any kind. Unfortunately this patient chose to undergo a thyroidectomy in another hospital and could not be followed further. Patient 22 (ref. 4, *Case 13*) had reacted with fever and leukopenia to thiouracil and later to thiobarbital. On each occasion therapy had to be discontinued and moderately severe hyperthyroidism returned. A dose of 25 mg. once daily of propylthiouracil was well tolerated and the metabolic rate fell to normal within a month. Finally, *Patient 27*, treated unsucessfully in 1942 with sulfadiazine (ref. 6), which caused a toxic reaction accompanied by fever, developed a recurrence of thyrotoxicosis following thyroidectomy. Thiouracil was given early in 1943 but treatment had to be discontinued on the tenth day because of drug fever (3). The persistent hyperthyroidism was subsequently fairly well controlled with iodine until the spring of 1945. Six weeks after iodine was discontinued hyperthyroidism of moderate severity returned; propylthiouracil in a dose of 25 mg. twice daily induced a satisfactory response without mishap.

These four cases provide clear evidence that propylthiouracil is well tolerated even by persons proved to possess a strong tendency to allergic sensitivity.

COMMENT

In view of the sensitivity reactions which sometimes attend the use of thiouracil and related antithyroid agents it has been apparent that efforts could profitably be directed toward reducing the incidence of these complications. One approach to the problem has been the simultaneous administration with thiouracil of accessory food factors, especially those thought from animal experiments to be concerned with hematopoiesis. Success with this method has not been notable to date. A second approach, the one upon which this report is based, has been to assay new compounds in animals in order to find substances with greater antithyroid effect but without a proportionally increased toxicity. Such studies led to the selection of ethyl- and propylthiouracil.

It is to be realized that such studies may not provide a valid basis for the selection of new drugs, for unless greater potency is accompanied by greater selectivity of action no advantage will have been found. As there is at present no means of predicting the likelihood of human sensitivity reactions from animal experiments alone this method of selection must be followed by clinical trial. This procedure was notably successful with the sulfonamide series of drugs wherein increased therapeutic effectiveness was associated with a decreased incidence of toxic reactions.

As was anticipated from preliminary work in rats and in chicks, small doses of ethyl- and propylthiouracil have proved effective in controlling all the clinical and laboratory manifestations of hyperthyroidism. In the 43 patients, eight of whom received both ethyl and propylthiouracil, there was but one toxic reaction; it was mild and disappeared when the drug was discontinued. This is a much more favorable experience than we have had with thiouracil or with thiobarbital, and may indicate not only greater antithyroid potency for these new thiouracil derivatives but also greater specificity. While some observers using thiouracil have had equally favorable results in small series of cases this comparison with the use

of thiouracil and thiobarbital under similar experimental conditions indicates that these derivatives represent an improvement over the parent compound. This conclusion is reinforced by the observation that patients tolerated ethyl- and propylthiouracil well although showing sensitivity to thiobarbital or to thiouracil itself. The satisfactory response induced by these drugs in such small doses and with such a low incidence of toxic reactions appears to justify their further trial.

It has been pointed out that an estimation of the minimal dose of an antithyroid compound which will be uniformly effective in the control of hyperthyroidism is most difficult. The two variables contributing to this difficulty are the individual differences in dosage requirement and the wide variation in the rate of response. Consequently it is not possible to state with accuracy the relative antithyroid activity of these new derivatives as compared with thiouracil. It has been the general impression that the initial dosage most commonly used *i.e.* 50 or 75 mg. of propylthiouracil daily provides a less intense antithyroid action, as manifest by the rate and degree of the metabolic response, than the commonly used doses of thiouracil, from 0.4 to 0.6 gm. daily. Likewise the maintenance doses of propylthiouracil used have only rarely given rise to myxedema and thyroid enlargement. The clinical results have, however, been entirely satisfactory and even if it be true that larger doses would have caused a somewhat more rapid response little is to be gained from such a practice. It is possible that the avoidance of excessive dosage in this study has contributed to the favorable results.

SUMMARY

Two derivatives of thiouracil which had been found to be approximately ten times as active as thiouracil in animal tests have been used for the treatment of hyperthyroidism. Fourteen patients were treated with 6-ethylthiouracil; eight of these and 29 others were given 6-*n*-propylthiouracil. The only side effect encountered was a single instance of an urticarial reaction from the ethyl derivative. It was estimated that 25 mg. of propylthiouracil at eight or twelve hour intervals is an adequate dose to restore metabolic equilibrium and that this state can be maintained by a daily dose of 25 to 50 mg. It is concluded that these compounds are about five times as active in man as thiouracil and are superior to thiouracil for the treatment of hyperthyroidism.

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LETTER

SOME OBSERVATIONS ON THE QUESTION OF HYPOPARATHYROIDISM OF DIENCEPHALIC ORIGIN

TO THE EDITOR:

THE PAPER of Nahum J. Winer on "Hypoparathyroidism of probable encephalopathic origin" in the *Journal of Clinical Endocrinology 5 (2)*: 86–91 (1945) induces me to add the following remarks:

Winer reports on a fundamentally important case of hypoparathyroidism with encephalographic evidence of cerebral damage particularly within the hypothalamic area. He says, "This appears to be the first instance of hypoparathyroidism coincidental with apparent organic cerebral pathology."

I should like to draw the author's attention to an article[1] of mine which appeared in 1928, and which obviously slipped his attention. This article dealt with the case of a girl, aged 20, who was suffering from both tetanic seizures and disturbances to be related to the diencephalic area. Three years prior to the onset of the tetanic manifestations the patient had had encephalitis lethargica. Apparently the hypothalamic lesion was attributable to the preceding encephalitis, and on its part had given rise to the outbreak of tetany. In the following I shall reproduce a brief description of the case history as given in my first report in the *Medizinische Klinik*. *Vide* also the reference to the "cerebral form of tetany," as I termed it then in my text-book, *The Diseases of the Endocrine Glands*, London, E. Arnold, 1935, p. 240; and 1944, p. 234.

The young girl in question was twenty years old. The family history and past history were negative. Three years earlier she had contracted encephalitis lethargica, as the result of which she had a bilateral reflex immobility of the pupils. Metabolic changes, pointing to a post-encephalitic hypothalamic lesion, were disturbances of the water and salt metabolism, resulting in a complete sodium chloride retention, and also a markedly low N-turnover, indicating a disturbed protein metabolism in the direction of the experimental findings of Leschke and Schneider who produced a damaging effect on protein metabolism through irritation of the diencephalon (these observations were confirmed by Freund and Grafe).

For three years, *i.e.*, since the encephalitis, the patient had a fever (axillary temperatures up to 38° C.), indicating a disturbance of thermal regulation. Accordingly a post-encephalitic lesion in the region of the tuber cinereum or of diencephalic centres above the tuber had to be suspected.

Investigation of the patient's blood chemistry revealed most striking fluctuations of calcium, potassium, magnesium, and sugar as well as of the dry blood residues from the normal average, a condition which might almost be termed "ataxy of the metabolism." For example, the blood serum calcium varied between 7 and 12 mg. per cent. After lumbar puncture the calcium value dropped from 11.5 to 7.4 mg. per cent; the composition of the spinal fluid was practically normal and its pressure only insignificantly raised. In view of the fact that the calcium showed a definite tendency to fall to low values found with both latent and manifest tetany, I assumed that in certain circumstances the disturbed calcium regulation might even give rise to genuine tetanic seizures. As mentioned above the patient did not only exhibit metabolic changes, but also had pronounced irregularities of her body temperature, and almost behaved like a poikilothermic and not a homeothermic individual. Whenever she

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[1] Gedanken und Erfahrungen ueber Pathogenese und Behandlung endekriner Krankheiten (Tetanie, endokrin-cerebrales Fieber, Morb. Basedowii), *Med. Klin. 24:* 685–688 (1928).

was exposed to external heat, her body temperature adapted itself, and the blood calcium dropped. Once, when the patient complained of pains in the legs, and an electric heat bath was applied, her rectal temperature rose from 38 to 41°. This enormous rise in temperature resulted in a corresponding drop of blood calcium, and this produced an extraordinarily severe tetanic fit. Henceforth it was always possible to bring about latent or manifest tetany by heat application, whereas in the intervals the patient did not even display signs of latent tetany such as Chvostek's or Trousseau's signs or increased irritability to electric stimulation.

I think that this history yields sufficient evidence to assume a direct relationship of the tetanic seizures to a diencephalic lesion of post-encephalitic origin.

HERMAN ZONDEK

The Biccur Cholim Hospital
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ANNOUNCEMENTS

THE SQUIBB AWARD

The E. R. Squibb & Sons Award of $1,000.00 was established in 1939, and was given first in 1940 to Dr. George W. Corner, in 1941 to Dr. Philip E. Smith, and in 1942 to Dr. Fred C. Koch. A special committee of five members of the Association chooses an investigator or investigators in the United States or Canada for one of the best contributions to endocrinology.

THE CIBA AWARD

The Ciba Award to recognize the meritorious accomplishment of an investigator not more than 35 years of age in the field of endocrinology was established in 1942, but no recipient was selected due to lack of time. The work cited may be either in the field of pre-clinical or clinical endocrinology. The Award is for $1,200.00. If the recipient should choose to use the Award toward further study in a laboratory other than that in which he is at present working, the Award will be increased to $1,800.00. The option is left entirely to the recipient.

Each member has the privilege of making one nomination for each Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions in endocrinology and by a bibliography of the nominee's most important publications, and reprints if possible. Five copies should be sent to the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City, Oklahoma, not later than March 15, 1946.

CARL R. MOORE, President
HENRY H. TURNER, Secretary

NATIONAL RESEARCH COUNCIL GRANTS FOR RESEARCH IN ENDOCRINOLOGY

The Committee on Research in Endocrinology, National Research Council, wishes to announce that requests for grants-in-aid during the fiscal period from July 1, 1946, to June 30, 1947, will be received until February 28, 1946. Application blanks may be obtained by addressing the Secretary, Division of Medical Sciences, National Research Council, 2101 Constitution Avenue, Washington 25, D. C. In addition to a statement of the problem and research plan or program, the Committee desires information regarding the proposed method of attack, the institutional support of the investigation and the uses to be made of the sum requested. No part of any grant may be used by the recipient institution for administrative expenses.

The Committee makes grants-in-aid of research in the general field of experimental and clinical endocrinology. However, applications for support of research in the problems of sex in the narrower sense cannot be given favorable consideration, and investigators seeking support in this field should direct their proposals to the Committee for Research in Problems of Sex of the National Research Council. The Committee on Research in Endocrinology, however, will continue to give consideration to the support of studies of the effect of sex hormones on non-sexual functions, e.g., on general metabolism and on the metabolism of steroid hormones.

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. *Collaborators:* F. A. DE LA BALZE, ISRAEL BRAM, CLARENCE D. DAVIS, ANNA FORBES, MURRAY B. GORDON, E. C. HAMBLEN, R. G. HOSKINS, JANET W. MCARTHUR, THOMAS H. MCGAVACK, J. R. REFORZO-MEMBRIVES, A. E. MEYER, E. C. REIFENSTEIN, JR., LEO T. SAMUELS, HAROLD WOOSTER, AND J. ZANARTU.

PANCREAS

BRUSH, J. M.

Initial stabilization of the diabetic child. *Am. J. Dis. Child. 67:* 429–444 (1944).

The author describes in detail a regimen that he has developed since May, 1931 at New York Babies Hospital for treating previously untreated juvenile diabetic patients. He cites the results obtained by this regimen in 39 patients. The author summarizes his hypothesis and regimen as follows. Children with diabetes mellitus who have had no previous treatment are capable of recovering an appreciable capacity to regulate the level of blood sugar regardless of the severity of the symptoms when treatment is commenced, provided the therapeutic regimen is directed toward the administration of insulin in such amounts as temporarily to relieve the islet apparatus of any contribution to the total insulin needed by the organism. The characteristic of submitting to the action of large and predictable amounts of exogenous insulin regardless of the apparent clinical severity of the disease has been termed insulin acceptance. Since maximal recovery, in terms of the amount of insulin required after stabilization, is achieved only when large amounts of insulin are administered during periods of regulation and recovery, the beneficial role of therapeutically administered insulin is readily conceived in terms of substitution of the hypodermic injection for the productive effort of an exhausted islet system which, though temporarily incapacitated, can be expected to recover a large fraction of its original competence provided it is not constantly goaded by the driving stimulus of hyperglycemia. Such substitution at a constant level constitutes insulin acceptance by the diabetic child as a probable total replacement mechanism. The regimen described is applicable to children of all ages and in a wide range of clinical states and provides a practical working guide which by standardizing therapy affords an opportunity for comparing one case with another; under favorable conditions the great majority of patients respond to it with striking uniformity. The patient is given a diet calculated on the basis of his age and weight; the diet so chosen is held constant during the period of intensive treatment with insulin and not altered according to his appetite. Hunger which develops during the adaptive period, after the disappearance of significant glycosuria, apparently represents a symptom of hypoglycemia rather than a true need for more food. After an interval of six to ten days during which the subject's daily requirement of insulin remains fairly constant at a high level (circa 60 to 70 units/100 grams dietary fat), moderate or severe shock marks initiation of the period of functional recovery. From this point on the rate of recovery, as measured by the decrease in the daily requirement of insulin, is so uniform as to be accurately predictable in the majority of instances. The similarity of clinical course, amounting virtually to reproducibility of therapeutic results, suggests the operation of physiologic and biochemical laws. The amount of insulin administered is decreased at a prescribed rate, which is calculated to steer the patient through the relatively narrow channel between glycosuria and insulin shock during the ensuing days of improving tolerance to carbohydrates and diminishing requirements of insulin. Mild shock, which is rarely disturbing to the child and never actually harmful, serves to indicate that enough insulin is being given. Improvement, once it has set in, may be terminated if the daily dose is reduced too abruptly because of the occurrence of severe shock; one loses ground by attempting to reduce the amount of insulin used as an end in itself. After hospitalization for 22 to 30 days the child is ready to be cared for at home, free from glycosuria, essentially free from shock and in a stable state on a full maintenance diet controlled by a single daily injection of insulin of between two and eight units. This regimen is not expected to modify

the long term result in these patients, and it is recognized that within a year or two after the onset of symptoms most patients will come to require more than 30 units of insulin a day, and many of them far more, regardless of the method by which they are treated in the early months after the onset. However, the author contends that his regimen, by contrast with a number of other methods of treating diabetic children, possesses certain advantages in that it holds the patient under close observation until he has reached a steady state, in that within this limit it confines him to the hospital a minimal length of time and in that it stabilizes his requirement of insulin at the lowest level compatible with efficient metabolic economy.—*E.C.R., Jr.*

ENGELHARDT, H. T., AND V. J. DERBES

Tumefaction of subcutaneous fat following the injection of insulin. A chemical and histologic study. *Am. J. M. Sc. 207:* 776–781 (1944).

In a 12-year-old child tumefaction of both deltoid regions appeared after about thee years of daily injections of unmodified insulin. After the lesions had increased slowly in size for six years a mass of material histologically indistinguishable from normal fat was removed by biopsy. Detailed chemical analyses of this material and of fatty tissue removed from the abdominal panniculus of an individual who had met sudden death were compared. There was very little difference in the non-diabetic and diabetic patients except that the diabetic fat was higher in unsaponifiable matter and phosphatids. The authors favor the hypothesis that the phenomenon of tumefaction is due to a local physiologic assimilatory effect of the insulin, with localized fat retention.—*E.C.R., Jr.*

HANDELSMAN, M. B.

Factors influencing the return of tolerance for glucose in middle-aged obese diabetics. *Am. J. M. Sc. 208:* 15–24 (1944).

An analysis was made of the carbohydrate tolerance of 55 ambulatory diabetics reporting to the Long Island College Hospital, following dietary management. All of the patients were markedly obese and over 40 years old at the onset of the diabetes. In the analysis, the blood and urine sugar levels, the response to the oral glucose tolerance test of Exton-Rose and the change in weight were evaluated. They conclude that: 1) obese patients who are over 40 years of age when glycemia and hyperglycemia first appear should be treated at once by strict dietary restriction aiming for reduction in weight, for disappearance of glycosuria and for a physiologic blood sugar level; 2) when such a regime is followed a remarkable return of tolerance to carbohydrate may occur; 3) to induce such a return of tolerance strict cooperation of the patient in following the diet is imperative; 4) when dietary management is not instituted in such patients until they have lost weight from neglect of treatment, ability to regain carbohydrate tolerance becomes permanently impaired; and 5) obese patients who have neglected treatment for many years are very difficult to manage unless they can be induced to lose weight by following a dietary regime. The authors believe that a kinetic viewpoint must be maintained toward these cases. The most important factors diminishing the ability of a patient to regain carbohydrate tolerance are: 1) lack of proper weight reduction; 2) delay over a period of years in treating the patient; 3) poor cooperation by the patient in following the weight-reducing regime; and 4) onset of the diabetes at an early age.—*E.C.R., Jr.*

KENNEDY, W. B., AND F. D. W. LUKENS

Alloxan diabetes. *Am. J. M. Sc. 207:* 550 (1944).

Rabbits were made diabetic by the intravenous administration of alloxan (200 mg. per kg. body weight). Ten animals which survived exhibited moderately severe diabetes (blood sugars ranged from 300 to 700 mg. per cent). Between 15 and 70 per cent of the calculated available dietary glucose was excreted in the urine; but the nitrogen excretion of the fasting diabetic rabbits was not significantly increased over that in the normal rabbit. The islands of Langerhans showed early widespread necrosis which progressed to atrophy. Although an elevated blood urea nitrogen was found at death in two rabbits, renal lesions (observed by others) were absent.—*E.C.R., Jr.*

LERMAN, J.

Insulin resistance. The rôle of immunity in its production. *Am. J. M. Sc. 207:* 354–360 (1944).

The blood from six patients with insulin resistance was examined by one or more of the following tests: a) ring precipitin, b) passive transfer, and c) biologic antagonism and was found by one or more of these tests to contain insulin antibod-

ies. The author concludes that: 1) antibodies to insulin appear to be antihormonic, 2) insulin resistance is dependent upon the appearance and concentration in the body of antibodies to insulin, 3) the return of normal insulin sensitivity is dependent upon the disappearance of the immune response, 4) the repeated administration of insulin, rather than its omission, offers a means for overcoming insulin resistance, 5) antibodies to insulin simulate antibodies to other hormones by being hormone-specific rather than species-specific, and 6) since patients recovering from insulin resistance usually become severe diabetics requiring 50 to 60 units of insulin daily, it is suggested that this represents the level of complete diabetes.—*E.C.R., Jr.*

MARTIN, H. E., D. G. SIMONSEN AND N. H. HOMANN

Time-activity curves of globin insulin with clinical applications. *Am. J. M. Sc., 208:* 321–332 (1944).

From studies on 36 patients the authors make the following observations concerning globin insulin: 1) the duration of action (dose of 10 to 80 units) varied with the dose and the severity of the diabetes, but in general was 14 to more than 24 hours—average 18 to 19 hours; 2) the peak of activity occurred between the 6th and the 10th hours; 3) the activity began within one hour of injection but increased slowly for the first three to five hours; 4) the time-activity function for a given dose was intermediate between regular and protamine zinc insulins as to duration and to total carbohydrate-handling ability; 5) the most satisfactory control of the blood sugar level of 14 patients receiving globin insulin (? in the morning) occurred when the patients were given a light breakfast, a mid-afternoon feeding, and in some instances a bedtime feeding; 6) globin insulin maintained fair to good control (except for occasional upsets) of the majority of 16 outpatients; 7) globin insulin has the following advantages: a) it allows better control of patients who are having severe nocturnal reactions with protamine zinc insulin, b) it allows better control of patients who are receiving before breakfast both regular and protamine zinc insulin (injected singly or combined), c) it has more carbohydrate-handling ability than protamine, with an earlier peak of action, and d) it is a clear solution which obviates mixing; and 8) globin insulin has the following disadvantages: a) it has too low an hourly carbohydrate-handling ability to cover the diet in most severe diabetics who take over 50 units; b) it has too short a duration of effect to cover the nocturnal insulin requirement of severe diabetics, and c) in an occasional patient it causes burning when injected.—*E.C.R., Jr.*

MILLER, H. C., R. D. JOHNSON AND S. H. DURLACHER

A comparison of newborn infants with erythroblastosis fetalis with those born to diabetic mothers. *J. Pediat. 24:* 603–615 (1944).

The histories and clinical data of 20 infants born to diabetic mothers at the New Haven Hospital, the Boston Lying-in Hospital and the New York Hospital are compared with those of 36 infants with erythroblastosis fetalis studied at the New Haven Hospital. The somatic and visceral changes are similar: an increased normoblastemia, extensive extramedullary erythroporesis, an hypertrophy of the heart, hyperplasia of the islands of Langerhans, adrenal enlargement, edema, macrosomia, and a tendency to hemorrhage in all the tissues of the body. Two striking differences between the two groups were found: infants with erythroblastosis fetalis frequently have enemia and jaundice and the Rh factor in the mother's blood is negative; whereas, infants born to diabetic mothers rarely have anemia or jaundice and the distribution of the Rh factor in their mothers is similar to that in the population at large. The relationship of the Rh factor in the mother to the similarities and differences in these two groups of infants is discussed.—*E.C.R., Jr.*

OPPENHEIMER, M. J., AND F. C. MANN

The intralobular pancreatic circulation. *Gastroenterology 3:* 218–226 (1944).

Casts of the circulation of the pancreases of dogs, cats, rabbits, guinea-pigs and white rats were made by intra-arterial injections of neoprene or neoprene mixtures followed by hardening with alcohol and the digestion of extravascular tissue with hydrochloric acid. The capillary bed was so great that the cast of the vascular tree thus obtained resembled the intact organ very closely when seen macroscopically. Widespread anastomoses were noted between acinar arterioles and also between recipient capillary regions, thus insuring "adequate circulation under widely varying circumstances." Islets varied considerably in size and were placed entirely on the arte-

rial side of the circulation. Blood may reach the acini directly or by way of the islet tissue, as dissections beginning at the interlobular arteries and ending at the intralobular capillaries have shown.—*T.H.McG.*

PARATHYROID

COBURN, D. E.

Severe osteitis fibrosa cystica with parathyroid tumor; report of case of 15 years' duration. *Am. J. Surg. 66:* 252–258 (1944).

A severe case of generalized osteitis fibrosa cystica due to parathyroid adenoma is reported, the tumor being located in the superior mediastinum. The case is remarkable in that the patient's symptoms date back over a period of nearly sixteen years during which time she suffered no less than four fractures and one operation for kidney stones. The skeletal involvement was extensive and included both patellas, a site which has not been previously reported. Her postoperative convalescence was marked by a fracture of the right femur, suggesting that in the postoperative care of these patients precautionary splinting might be applied to bones of the extremities which are extensively involved until some degree of recalcification has occurred. —*Author's Summary.*

THYROID

BRAM, I.

Thyroid disease in youngsters under age sixteen; comments on a series of 1,200 cases. *Arch. Pediat. 61:* 300–310 (1944).

During a period of 33 years, the author has observed a series of nearly 17,000 cases of thyroid disease, of which approximately 1200 (7%) occurred in children under age sixteen. The author gives a general account of the disease in children and concludes: 1) The disease (with and without goiter) differs from that in adults; treatment also differs since surgery is rarely required. 2) Differential diagnosis of thyroid disease in children is not easy since many conditions to be excluded (e.g. paroxysmal tachycardia, anemia, anxiety neurosis, undernutrition, primary heart disease, chorea, intestinal parasites) alter the basal metabolic rate, and since congenital defects (cysts or "pop-eyes") may be present. 3) Hypothyroidism and hyperthyroidism are not necessarily associated with goiter, and vice versa. 4) The etiological factors in simple sporadic goiter in children are heredity, faulty dietetic and hygienic habits, local or general infections, and a singular incapacity of the thyroid to meet the requirements of growth and development. 5) Once discoverable etiological factors are eliminated, the specific medicament of hypothyroidism and sporadic simple goiter in children is not iodine but thyroid substance. 6) The hyperthyroidism of exophthalmic goiter (Graves' disease) is not due to goiter but to a constitutional neuroendocrine dysfunction in which the thyroid gland is not etiologically, but sequentially implicated. The etiological factor in the average case appears to be a congenital predisposition (Graves' constitution) upon which is superimposed an exciting cause in the form of a psychic trauma, an infection, continued tension or overwork. 7) Since exophthalmic goiter is a psychosomatic syndrome, psychotherapy is a major factor in treatment within a broad regime of patiently applied therapy.—*E.C.R., Jr.*

BRUCH, H., AND D. J. MCCUNE

Mental development of congenitally hypothyroid children; its relationship to physical development and adequacy of treatment. *Am. J. Dis. Child. 67:* 205–224 (1944).

The authors have examined the effect of adequate treatment with thyroid hormone as judged by physical progress on the mental development of congenitally hypothyroid children. Their evaluation is based on a review of the lierature and on longitudinal studies of 23 children (7 boys and 16 girls) who attended the Vanderbilt Pediatric Clinic of the New York Babies Hospital. These children were selected on the basis of: a) adequate data for appraisal, b) unequivocal diagnosis based on physical response to thyroid hormone treatment and its withdrawal. Determinations of skeletal height, bone age, serum cholesterol and urine creatine were found to be of value in making the diagnosis. Retardation of bone age of more than six months was present in only five cases at the time their mental status was determined. Thirteen children were under one year of age, the youngest was three months of age, four children were between one and three years of age, and six were more than three when therapy was started. Mental development of these patients was evaluated by psychometric testing at intervals. Two patterns of progress were observed: 1) development following closely the lines of expected

progress; and 2) arrest of development at a low level. Physical development, particularly skeletal maturity, was related to the age at the beginning of and the adequacy of treatment; mental development, on the contrary, progressed more or less independently of treatment and tended to become arrested in children of low intelligence. Six cases are presented in detail. The authors conclude: 1) although there is a distinct relation between early, adequate treatment and subsequent physical development, a comparable relation is absent, or at most highly imperfect, with respect to mental attainment; 2) the intellectual inferiority presented by many congenitally hypothyroid children is not in all cases due to lack of thyroid hormone, but in some instances at least is due to a concomitant defect in cerebral development which cannot be modified by glandular treatment; 3) in other cases, however, retarded growth of the brain may be due to postnatal lack of thyroid, and hence early diagnosis and treatment is important; 4) the functional development of congenitally hypothyroid children before treatment supplies an index of their capacity for future mental development, since those with the capacity for good intellectual development are much less retarded than those whose subsequent progress will be poor; 5) the prognosis for intellectual development must be guarded in advance of therapeutic trial; and 6) too vigorous use of thyroid therapy can have distinctly undesirable consequences, since deterioration of performance quantitatively measurable by psychometric tests and serious disorders of behavior may occur when excessive amounts are administered.—*E.C.R., Jr.*

CHESLEY, L. C.

Observations on the absorption, apparent volume of distribution and excretion of thiourea. *J. Clin. Investigation 23:* 856–858 (1944).

In suitable normal subjects, the blood, urine, stools, and milk were analyzed for their content of thiourea at periodic intervals following a test dose of 1000 mg. of thiourea. Urea and thiourea clearances were simultaneously performed. From these data, attempt was unsuccessfully made to estimate the total body water. In the course of the experiments it was found that the renal clearance of thiourea is very close to that of urea; that thiourea enters the cerebrospinal fluid, probably slowly; that the concentration of thiourea in serum and in breast milk is nearly the same; that when single doses of 1000 mg. of thiourea are given by mouth, about 25 per cent cannot be recovered; and that none of the ingested thiourea appears in the feces within three days following its administration.—*T.H. McG.*

CHU, J. P.

The influence of thyroid on pregnancy and parturition in the rabbit. *J. Endocrinol. 4* (2): 109–114 (1945).

Unlike Krichesky (1939) the author finds that the thyroid gland is necessary for normal gestation in the rabbit. If thyroidectomy was performed at an early stage of pregnancy resorption and abortion of the embryos occurred, while if the operation was performed at a late stage of pregnancy stillborn young were delivered. When pregnancy was induced in thyroidectomized rabbits the embryos were either resorbed or aborted or prolongation of gestation resulted owing to retention of fetuses. The newborn fetuses of thyroidectomized animals were usually dead. Thyroidectomized rabbits fed with desiccated thyroid following the operation gave normal viable litters in two out of four cases. Superfecundation was successfully induced in thyroidectomized rabbits by injecting pituitary gonadotrophin immediately after coitus. The large number of embryos thus produced was usually resorbed. Resorption could be prevented by administration of desiccated thyroid started immediately after mating. The author concludes that the thyroid hormone is essential in maintaining the vitality of the embryos. The prolongation of pregnancy is assumed to be due to over-production of estrogen in the absence of the thyroid. This is thought to be due to an increase in the production of follicle stimulating hormones of the pituitary gland.—*L.T.S.*

DALTON, A. J., H. P. MORRIS AND C. S. DUBNIK

Changes in the organs of female C3H mice receiving thiourea. *J. Nat. Cancer Inst. 5:* 451–454 (1945).

Thiourea was added to the diet of virgin C3H mice when they were 11 months of age. The animals were maintained on this regimen until they developed spontaneous mammary cancer, when they were killed and the ovaries, uteri, adrenals, and thyroids studied histologically. The thyroids showed the expected hyperplasia, red blood cells were found within

their follicles, and a granular, greenish yellow pigment appeared in the cytoplasm in the distal portion of the follicular cells. No changes were seen in the uteri, but a general degeneration of the follicles and ova was noted in the ovaries, and there was a decrease in the osmiophilic material of the adrenal cortices.—*Courtesy Cancer Research.*

GABRILOVE, J. L., M. J. KERT AND L. J. SOFFER

The use of thiouracil in the treatment of patients with hyperthyroidism. *Ann. Int. Med. 23:* 537–558 (1945).

Thiouracil was employed in the treatment of 51 patients with hyperthyroidism and in three patients with non-toxic goiter. During the first four to six weeks of treatment the patients were hospitalized and given thiouracil in a dosage of 0.4 to 1.0 gm. After discharge, the dosage of thiouracil was reduced to 0.1 or 0.2 gm. daily and the patients followed in the outpatient department. Thiouracil was continued for a variable length of time, the longest period of continuous treatment being ten months. Thirty-three of the patients with hyperthyroidism (29 cases of primary hyperthyroidism and four of recurrent hyperthyroidism) were treated successfully with thiouracil. Three patients with hyperthyroidism were successfully prepared for operation with thiouracil. Four patients were classified as showing lack of response to thiouracil. Three of these patients received the drug for no more than 30 days; in the fourth, the dosage of thiouracil had to be sharply reduced because of leukopenia after an initially favorable response, and the B.M.R. rose again. These patients were operated upon successfully after preparation with iodine. Severe toxic reactions forced the discontinuance of thiouracil therapy in 11 cases. Thirty-one per cent of the patients developed some toxic manifestation. Conjunctivitis was observed in 5 cases; edema, 1; drug fever, 4; leukopenia, 1; and agranulocytosis, 6. One case of agranulocytosis was fatal. Liver and kidney function tests remained normal throughout the course of treatment. In the authors' opinion, the indications for the use of thiouracil therapy are: (1) Preparation of iodine-fast patients for surgery; (2) Treatment of individuals with hyperthyroidism, in whom for some reason surgery is deemed hazardous; (3) Treatment of cases of recurrent hyperthyroidism who have been operated upon twice or more.—*J.M.*

LAHEY, F. H., E. C. BARTELS, S. WARREN AND W. A. MEISSNER

Thiouracil—its use in the preoperative treatment of severe hyperthyroidism. *Surg., Gynec. and Obst. 81:* 425–439 (1945).

Clinical observations on 190 severely hyperthyroid patients prepared for operation with thiouracil are reported. It was found that approximately one day of treatment with 0.6 gm. of thiouracil was required for each percentage of elevation in the basal metabolic rate. Patients treated previously with iodine required a slightly longer period of treatment to return the metabolic rate to normal. Patients whose hyperthyroidism was of no more than two to three months' duration responded more quickly to treatment than did those whose disease had been present for a longer time. In the earlier patients prepared for operation with thiouracil alone, a troublesome surgical complication was encountered. The thyroid gland proved to be extremely friable, rendering hemostasis so difficult that it was sometimes impossible to do a sufficiently radical thyroidectomy. This difficulty was overcome by administering iodine during the three week period immediately before operation. For two weeks iodine and thiouracil were administered simultaneously and during the final week iodine alone was given. In patients adequately treated with thiouracil the pulse and blood pressure remained constant during operation, and postoperative reactions did not occur. Toxic reactions developed in 11% of the patients. These consisted of: granulocytopenia, 9 patients; fever, 7; skin eruption, 4; scleredema, 2; and swelling of the salivary glands, 1. Four of the patients with granulocytopenia developed agranulocytic angina and one patient died. Seventy-seven glands resected from this group of patients were subjected to pathological study. It was not possible to distinguish a thiouracil-treated specimen from a hyperplastic gland which had no previous thiouracil therapy. When iodine was used in conjunction with thiouracil the majority of specimens showed histologic evidence of involution.—*J.M.*

PUPPEL, I. D., H. T. GROSS, E. K. MCCORMICK AND E. HERDLE

The rationale of calcium, phosphorus and vitamin D therapy in clinical hyperthyroidism. *Surg., Gynec. and Obst. 8:* 243–265 (1945).

Besides an extensive review of the pertinent clinical and experimental literature, the authors present studies on the effects of calcium, phosphorus and vitamin D therapy on the calcium balance of 11 patients suffering from hyperthyroidism. An average loss of 459 milligrams of calcium per day occurred in these patients maintained on a low calcium intake (averaging 474 mgm. per day over a period of 90 days). A positive calcium balance averaging 352 mgm. per day was achieved in the patients given an adequate intake of calcium from various sources (averaging 2410 mgm. per day over a period of 81 days). Retention occurred whether the calcium was fed or given parenterally. Similar changes occurred in the phosphorus balance. Calcium gluconate, calcium lactate with drisdol, intravenous calcium chloride, and dicalcium phosphate with viosterol were administered to groups of patients as supplements to the high calcium and high phosphorus diets. All proved effective in maintaining retention of calcium and phosphorus, but dicalcium phosphate with viosterol promoted 200–1000% greater retention than did any of the other forms. The ordinary hyperthyroid patient requires about two grams of calcium per day to maintain positive calcium balance. This is at least twice the optimal calcium requirement for normal adults. Three grams daily is a more adequate amount to restore depleted calcium. Phosphorus requirements are similarly increased. The authors have been impressed by the smooth postoperative course and absence of thyroid storms exhibited by their patients who have received adequate calcium, phosphorus and vitamin D in addition to the older preoperative regimen.—*J.M.*

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